IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BRISTOL-MYERS SQUIBB COMPANY,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 10-805-CJB
	)	
TEVA PHARMACEUTICALS USA, INC.,	)	
	)	
Defendant.	)	

Jeffrey B. Bove, Esquire and Chad S.C. Stover, Esquire of NOVAK DRUCE CONNOLLY BOVE + QUIGG LLP, Wilmington, DE.

Of Counsel: Paul H. Berghoff, Esquire, Joshua R. Rich, Esquire, Jeremy E. Noe, Esquire, and Alison J. Baldwin, Esquire of McDONNELL BOEHNEN HULBERT & BERGHOFF LLP, Chicago, IL.

Attorneys for Plaintiff.

John C. Phillips, Jr., Esquire and Megan C. Haney, Esquire, of PHILLIPS, GOLDMAN & SPENCE, P.A., Wilmington, DE.

Of Counsel: George C. Lombardi, Esquire, Lynn MacDonald Ulrich, Esquire, Ivan M. Poullaos, Esquire, Julia Mano Johnson, Esquire, John R. McNair, Esquire, and Elizabeth J. Thompson, Esquire of WINSTON & STRAWN LLP, Chicago, IL.

Attorneys for Defendant.

MEMORANDUM OPINION

February 11, 2013
Wilmington, Delaware

BURKE, United States Magistrate Judge

INTRODUCTION

Plaintiff, Bristol-Myers Squibb Company ("BMS"), markets a medication under the trade name Baraclude® for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication, and either evidence of persistent elevations in serum aminotransferases or histologically active disease. (D.I. 135, ex 1 (hereinafter "Uncontested Facts") at ¶¶ 21–23) The medication contains 0.5 mg and 1 mg of the compound entecavir in tablet form. (*Id.* at ¶ 22) The United States Food and Drug Administration's ("FDA") Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") lists United States Patent No. 5,206,244 (the "'244 Patent") in connection with BMS's Baraclude product. (*Id.* at ¶ 9)

Defendant Teva Pharmaceuticals USA, Inc. ("Teva") filed an Abbreviated New Drug Application ("ANDA") seeking approval to market a generic version of Baraclude for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication, and either evidence of persistent elevations in serum aminotransferases or histologically active disease. (*Id.* at ¶¶ 24–25) On September 22, 2010, BMS initiated this litigation against Teva in connection with the Paragraph IV certification contained in Teva's ANDA. (*Id.* at ¶ 34)

On August 8, 2012, the parties jointly consented to the Court's authority to conduct all proceedings in this case, including trial, the entry of final judgment, and all post-trial proceedings. (D.I. 132) The Court held a bench trial from October 15, 2012 to October 18, 2012. (D.I. 142; D.I. 143; D.I. 144; D.I. 145 (collectively, "Tr.")) At trial, Teva contended that claim 8 of the '244 Patent is invalid as obvious under 35 U.S.C. § 103 ("Section 103"). (D.I. 151 at ¶ 8) Teva also asserted that the '244 Patent is unenforceable based on inequitable conduct

committed by certain former BMS employees before the U.S. Patent and Trademark Office ("PTO"). (Uncontested Facts at ¶ 37; D.I. 151 at ¶ 8) The parties completed post-trial briefing on December 17, 2012. (D.I. 150; D.I. 151; D.I. 156; D.I. 157) The 30-month stay imposed by 21 U.S.C. § 355(j)(5)(B)(iii) on the FDA in relation to granting final approval of Teva's ANDA expires on or around February 12, 2013. (Uncontested Facts at ¶ 30)

As explained below, the Court finds in favor of Teva as to invalidity, finding that Teva has demonstrated by clear and convincing evidence that Claim 8 of the '244 Patent is invalid as obvious under Section 103. The Court finds in favor of BMS with respect to inequitable conduct, finding that Teva has not met its burden to prove that certain then-BMS employees committed inequitable conduct before the PTO regarding the application that led to the issuance of the '244 Patent.

Pursuant to Federal Rule of Civil Procedure 52(a), the Court hereby presents its findings of fact and conclusions of law.

FINDINGS OF FACT

I. BACKGROUND

A. Nature and Stage of Proceedings

1. BMS is the holder of New Drug Application ("NDA") No. 21-797 for a medication in tablet form containing 0.5 mg and 1 mg of entecavir. (Uncontested Facts at ¶ 21)

2. On March 29, 2005, the FDA approved the marketing of the medication described in NDA No. 21-797 for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication, and either evidence of persistent elevations in serum aminotransferases or histologically active disease. (*Id.* at ¶ 22)

3. BMS sells the medication described in NDA No. 21-797 in the United States under the trade name Baraclude. (*Id.* at ¶ 23)

4. Teva has filed ANDA No. 202122 seeking approval to market a generic version of Baraclude. (*Id.* at ¶ 24) Teva's ANDA application, containing a Paragraph IV certification, constituted an act of infringement of claim 8 of the '244 Patent under 25 U.S.C. § 271(e)(2), to the extent that claim was found to be valid and enforceable. (*Id.* at ¶ 39)

5. The thirty-month stay barring Teva from marketing its drug expires on or around February 12, 2013. (*Id.* at ¶ 30; 21 U.S.C. § 355(j)(5)(B)(iii); 21 C.F.R. § 314.107(b)(3))

B. Key Players

6. Dr. Robert Zahler is one of two named inventors on the '244 Patent. (JTX 1)[1] Dr. Zahler received a Ph.D. in organic chemistry from the University of California, Berkeley in 1977. He then completed four years of post-doctoral research in the areas of physical organic chemistry and synthetic methodologies and total synthesis of natural products at University College London and the California Institute of Technology. (JTX 51; Tr. 757:15–758:3) Dr. Zahler was hired by BMS's predecessor, E.R. Squibb and Sons, Inc. ("Squibb") in 1981, and worked there and at BMS until 2007, when he was laid off by BMS.[2] (JTX 51; Tr. at 513:20–514:4) Dr. Zahler currently operates a consulting business. (JTX 51; Tr. 514:5–12)

7. Dr. William A. Slusarchyk is the other named inventor on the '244 Patent. (JTX

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[1] When used in this Memorandum Opinion, "PTX" refers to BMS's trial exhibits; "DTX" refers to Teva's trial exhibits; "JTX" refers to the parties' joint trial exhibits; "PDX" refers to BMS's demonstrative exhibits; and "DDX" refers to Teva's demonstrative exhibits.

[2] In 1989, Squibb merged with Bristol-Myers Company, forming BMS. (Uncontested Facts at ¶ 14)

1) Dr. Slusarchyk received a Ph.D. in organic chemistry from Penn State in 1965. (Tr. 903:14–904:5) He was employed at Squibb, and then BMS following the merger, for approximately 37 years. (Tr. 904:13–23)

8. Stephen Venetianer was a patent prosecuting attorney at BMS from 1980 until December 1990. (Tr. 977:6–15) Mr. Venetianer filed U.S. Patent Application No. 07/599,568 (the "'568 Application") on October 18, 1990 on behalf of Drs. Zahler and Slusarchyk; that application was the first application for the '244 Patent. (JTX 2.0004–107)

9. Stephen Davis was a patent prosecuting attorney at BMS from 1973 until his retirement in 2005. (Tr. 674:18–20) Mr. Davis was Mr. Venetianer's successor in prosecuting the '568 Application. (Tr. 675:16–23) On September 20, 1991, Mr. Davis filed U.S. Patent Application 07/763,033 (the "'033 Application") as a continuation-in-part of the '568 Application, which led to the issuance of the '244 Patent. (Tr. 677:12–16; JTX 1.0001; JTX 3.0001, .0244)

10. Dr. Clayton Heathcock is an expert witness proffered by Teva in the field of organic and medicinal chemistry. (Tr. 120:5–7) Dr. Heathcock received a Ph.D. in organic chemistry from the University of Colorado in 1963 and completed one year of post-doctoral study at Columbia University. (JTX 149.0002; Tr. 100:4–11) He is an Emeritus Professor of Chemistry at the University of California, Berkeley, where he was hired as assistant professor in 1964. (JTX 149.0002; Tr. 98:20–23; 101:1–6) During the course of his career, the primary area of Dr. Heathcock's scientific research was synthetic organic chemistry, which is a field involving the making of complicated compounds. (Tr. 102:19–103:9; 109:6–7) Dr. Heathcock also completed projects in the field of medicinal chemistry and published in the area of physical

organic chemistry. (Tr. 103:9–13) He has experience training medicinal chemists who went on to work for pharmaceutical companies. (Tr. 109:7–15) Since the 1960s, Dr. Heathcock has worked as a consultant for various pharmaceutical companies in regards to their medicinal chemistry programs. (Tr. 110:16–115:12) From approximately 1986–1991, Dr. Heathcock consulted with Abbott Laboratories concerning an antiviral nucleoside analog program. (Tr. 114:7–117:9) However, Dr. Heathcock has not otherwise focused his research or work on nucleoside analogs. (Tr. 243:17–23; 244:9–11; 244:18–20; 245:7–13) Although Dr. Heathcock has frequently testified about medicinal chemistry, this is the first case involving nucleoside analogs in which he has testified. (Tr. 247:11–19)

11. Dr. Chloe L. Thio is an expert witness proffered by Teva in the area of hepatitis B infection and its treatment. (Tr. 394:18–20) Dr. Thio is a physician and Associate Professor of Medicine at John Hopkins University. (JTX 148; Tr. 384:11–14) She received an M.D. from Yale University in 1992. (Tr. 385:18–20) Dr. Thio predominantly treats patients with infectious diseases, specializing in the treatment of hepatitis and HIV infections. (Tr. 387:13–18) Her research focuses mainly on hepatitis B and HIV-hepatitis B co-infection. (Tr. 389:7–8)

12. Dr. Bud C. Tennant is an expert witness proffered by BMS in the areas of woodchuck hepatitis virus, woodchuck research, and the testing of antiviral drugs on woodchucks. (Tr. 988: 13–17) Dr. Tennant received a Ph.D. in veterinary medicine from the University of California in 1959. (JTX 147; Tr. 983:14–18) He is currently the James Law Professor of Comparative Medicine at Cornell University. (JTX 147; Tr. 985:3–9) For the past thirty years, Dr. Tennant's primary research work has been done on the woodchuck model of hepatitis B infection. (Tr. 985:20–24)

13. Dr. Stewart Schneller is an expert witness proffered by BMS in the area of nucleoside analog research. (Tr. 1052:24–1053:3) Dr. Schneller received a Ph.D. in organic chemistry from Indiana University in 1968. (JTX 145; Tr. 1045:23–1046:7) He then completed three years of post-doctoral work in organometallic chemistry. (JTX 145; Tr. 1045:24-1046:12) Dr. Schneller is currently a Professor of Chemistry and Biochemistry at Auburn University. (JTX 145; Tr. 1047:6–8) His research is in the field of nucleoside chemistry, primarily carbocyclic nucleosides. (Tr. 1047:18–20)

14. Michael E. Tate is an expert witness proffered by BMS in the fields of financial and economic analysis. (Tr. 1271:20–22) Mr. Tate received a M.S. in industrial administration from Purdue University in 1987. (JTX 146; Tr. 1269:6–10) He is currently the Vice President at Charles River Associates, an international business consulting firm. (JTX 146; Tr. 1269:11–17)

15. Dr. Robert Gish is an expert witness proffered by BMS in the area of the treatment of hepatitis B. (Tr. 1324:11–13) Dr. Gish received an M.D. from the University of Kansas in 1980. (JTX 144.0002; Tr. 1317:16–19) He is a physician and is currently the co-director of the Center for Hepatobiliary Disease and Abdominal Transplantation, Chief of the Section of Hepatology, and Clinical Professor of Medicine at the University of California, San Diego. (JTX 144.0002; Tr. 1318:11–18) Dr. Gish treats patients with liver disease, including hepatitis B. (Tr. 1319:7–22) Dr. Gish's research focuses on viral hepatitis, which includes hepatitis B and hepatitis C. (Tr. 1321:24–1322:9) Dr. Gish has consulted with several pharmaceutical companies regarding hepatitis B drugs, including BMS regarding its development of entecavir. (Tr. 1322:10–1323:8)

C. The '244 Patent and the Claimed Invention—Entecavir

16. The '244 Patent, entitled "Hydroxymethyl (Methylenecylopentyl) Purines and Pyrimidines," issued on April 27, 1993, naming Dr. Zahler and Dr. Slusarchyk as the inventors, and listing Squibb as the assignee. (JTX 1; Uncontested Facts at ¶ 10)

17. The '244 Patent expires on February 21, 2015. (Uncontested Facts at ¶ 7)

18. The '244 Patent claims a genus of chemical compounds known as nucleoside analogs. (PTX 1; D.I. 150 at ¶ 2; D.I. 151 at ¶ 2; Tr. 122:7–11) Natural nucleosides are chemical compounds made up of a sugar portion[3] and a base portion and are part of the basic building blocks of DNA and RNA. (Tr. 130:10–24; 133:3–24; 1059:8–18) When the sugar portion contains five carbon atoms that are bonded to each other in a ring-like fashion, this is referred to as a "cyclopentane ring" (the "five-membered ring"). (Tr. 123:14-20) When this ring includes an attached oxygen atom, it is known as a "furanose ring." (Tr. 165:19–166:14)

19. Natural nucleosides are the starting point for antiviral research. (Tr. 1065:21–1068:14) Nucleoside analogs are chemical compounds that are designed by chemists to mimic natural nucleosides, but have been modified in some way. (Tr. 136:18–137:12) Many antiviral drugs are nucleoside analogs. (Tr. 139:22–140:5; 1065:11–20) This is because nucleoside analogs interfere with the process by which a virus reproduces itself. (Tr. 139:1–21)

20. Guanosine is one of four common nucleosides. (Tr. 135:16–136:3; DDX 42)

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[3] The sugar portion of a nucleoside may also be referred to as the carbohydrate portion, but the two terms mean the same thing; carbohydrate and sugar are synonyms in this context. (Tr. 130:14–16)

Guanosine is made up of a heterocyclic sugar portion (called ribose) and a heterocyclic base (called guanine).[4] (Tr. 130:10–24; 131:1–9; DDX 40) The remaining three common nucleosides are adenosine, uridine, and cytidine. (Tr. 135:16–136:3; DDX 42)

21. The sugar portion of a nucleoside contains an oxygen at the 2 prime (also referred to as "2'") position. (Tr. 133:5–9; DDX 41, 42) A 2' deoxynucleoside is a nucleoside that lacks an oxygen at the 2 prime position on the sugar portion of the compound, but is identical in other respects. (Tr. 133:5–19; DDX 41; PDX 531) There are four common deoxynucleosides involving adenine, guanine, thymine, and cytosine. (Tr. 136:3–17; DDX 43) Deoxynucleosides are the building blocks from which DNA is made, while nucleosides are the building blocks from which RNA is made. (Tr. 133:20–134:3)[5]

22. The genus of purine nucleoside analogs claimed by the '244 Patent all must have what is referred to as an "exocyclic methylene group" at the 5 prime position[6] of the sugar portion, which group is depicted in the circle below:

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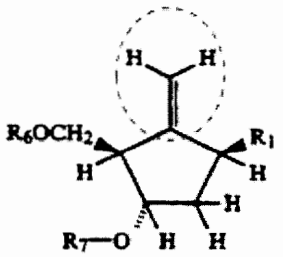
[4] "Heterocyclic" means that the atoms in the compound connect to form a ring shape, and not all of the atoms are carbon. (Tr. 130:20–24) When all of the atoms are carbon, this is called a "carbocyclic ring." (Tr. 40:20-21)

[5] DNA, or deoxynucleic acid, is a long polymer made up of deoxynucleosides that contains the genetic information that a cell needs to exist and replicate. (Tr. 134:8–17; 1054:3–9; 1055:2–7) RNA, or ribonucleic acid, is a long polymer made up of nucleosides that puts the information contained in DNA into action. (Tr. 134:18–135:4; 1054:3–11)

[6] The 5 prime position is also sometimes referred to as the 6 prime position, but they mean the same thing: the position at the top of the five-membered ring. (Tr. 33:14–24)

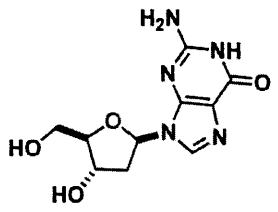


(D.I. 150 at ¶ 2; JTX 1) "Exocyclic" means something that is attached outside of the five-membered ring; an exocyclic methylene group is a carbon-carbon double bond that is attached outside of that ring. (Tr. 210:16-17; 1077:2–18)

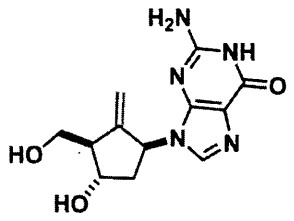
23. The only claim of the '244 Patent asserted in this case is claim 8, which covers the chemical compound entecavir. (D.I. 150 at ¶ 2; 151 at ¶ 3)

24. Teva has stipulated to infringement of claim 8 of the '244 Patent, to the extent that claim 8 is found to be valid and enforceable. (Uncontested Facts at ¶¶ 39–40; D.I. 135, ex. 7)

25. Entecavir is a carbocyclic nucleoside analog. (Tr. 116:1–6) Entecavir mimics the natural nucleoside 2' deoxyguanosine, in that the compounds have identical bases, but the sugar portion of entecavir is different from that of the natural nucleoside. (D.I. 151 at ¶ 3; Tr. 137:13–24; 1074:7–11) While the sugar portion of 2' deoxyguanosine has an oxygen atom at the 5 prime position, entecavir has a carbon-carbon double bond at the 5 prime position, instead of an oxygen atom. (D.I. 151 at ¶ 3; Tr. 137:20–24; 1077:2–1078:10; DDX 44) A chemical name for entecavir is [1S-(1α,-3α,4β)]-2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one. (Uncontested Facts at ¶ 16) The natural nucleoside 2' deoxyguanosine and entecavir can depicted as follows:



deoxyguanosine
(dG)



entecavir

(D.I. 150 at ¶ 3)

26. The Abstract of the '244 Patent states that "antiviral activity" is exhibited by the claimed compounds. (JTX 1) The patent's specification states that the claimed compounds "are antiviral agents that can be used to treat viral infection in mammalian species such as . . . humans . . . ." (JTX 1.0003, col. 3:62–66) The patent further states that the compounds are effective against particular viruses including herpes simplex virus 1 ("HSV-1") and herpes simplex virus 2 ("HSV-2"), and that "[t]hey are also believed to be active against a variety of other" viruses including hepatitis B virus. (*Id.*, col. 3:67–4:41)

27. The '244 Patent contains a table depicting *in vitro* test results[7] for claimed compounds, including entecavir, displaying activity against herpes family viruses and HIV. (JTX 1.0027; Tr. 146:13–148:12) The patent does not include results from any *in vivo* testing against any virus. (Tr. 148:15–19) Nor does the patent include test results of any kind against hepatitis B. (Tr. 148:20–149:1; 455:3–13)

28. In 2005, entecavir, marketed by BMS as Baraclude, was approved by the FDA for the treatment of chronic hepatitis B virus infections. (Uncontested Facts at ¶¶ 21–23; DTX 35; Tr. 140:6–11)

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[7] *In vitro* testing means testing done in a laboratory. (Tr. 455:19–456:2) In contrast, *in vivo* testing is done in living organisms. (Tr. 148:15–18)

II. FINDINGS OF FACT RELEVANT TO OBVIOUSNESS

A. Approaches for Discovery of New Drugs

29. In the late 1980s, a medicinal chemist would generally take one of three approaches to attempt to discover new drugs. (DDX 29; Tr. 140:12–142:22)

30. The traditional approach—the easiest and probably the most common approach—was the modification of a known lead compound. (Tr. 140:24–141:8; 144:8–17) A chemist utilizing this approach makes changes to an existing compound, known as a "lead compound," in an attempt to create a new compound with improved antiviral properties. (Tr. 140:24–141:10; 1147:2–12; 1149:2–23) This traditional approach is based upon a tenet known as "structure activity relationship" ("SAR"). (Tr. 145:4–19; 1146:13–1147:1) That is, a chemist working with a lead compound to make new compounds understands that if he has "two compounds that are similar in structure, [he will expect that] they will have similar activity." (Tr. 145:4–14) At the beginning of this traditional SAR approach, a medicinal chemist typically does not know anything about "the mechanism of action of the drugs involved;" the idea is to learn about the compounds through the testing process. (Tr. 1150:4–14)

31. The second approach to discovering new drugs involves random screening of compounds against an *in vitro* assay to find a lead compound. (Tr. 141:11–142:7)

32. The third approach to discovering new drugs, the most difficult, is known as the biological approach. (Tr. 142:8-22) This approach entails learning about the biology of a disease and, from there, attempting to design a drug that targets the disease. (*Id.*)

B. The Invention of Entecavir

33. In 1985, Squibb made Dr. Zahler the leader of its effort to discover new antiviral

drugs. (Tr. 763:12–14; 764:3–17) At this time—the mid-1980s—Dr. Zahler had a Ph.D. in chemistry, a few years of medicinal chemistry experience, and no experience with nucleoside analogs. (Tr. 757:11–760:5; 763:12–764:17; 1447:12–1448:9) Dr. Zahler, along with other members of his team who worked the project with him, began by reading the scientific literature and patents in the antiviral nucleoside analog field. (Tr. 764:18–765:18)

34. While still reviewing the literature, Dr. Zahler and his team selected acyclovir as their lead compound. (Tr. 771:4–23) Acyclovir was chosen as a lead compound because it was a safe drug that was on the market and was effective in treating HSV-1, HSV-2 and varicella-zoster virus ("VZV"). (Tr. 772:3-7) Dr. Zahler and his team then spent a year making thirty to forty acyclic nucleoside analogs, using acyclovir as a lead compound. (Tr. 776:20–777:6; PTX 181–225, 234, 235) None of the analogs showed enough antiviral activity to support further development as a drug candidate. (Tr. 779:17–780:13; PTX 181–225, 234, 235)

35. Using the traditional drug discovery approach—making structural changes to lead compounds that exhibited antiviral activity—Dr. Zahler had invented a carbocyclic nucleoside analog called lobucavir (also known as "BMS 180194" and "SQ-33054") with a four-membered carbocyclic ring in the place of a sugar. (Tr. 560:5-9; 801:23–24; 882:20–884:5; PTX 622.0006–07)

36. By 1989, after his team had failed to succeed using the traditional drug discovery approach, Dr. Zahler decided to try a different approach, which led to his conception of entecavir. (Tr. 571:22-572:9; 787:11–19) Dr. Zahler first came up with the idea for entecavir in his head and drew it out on paper. (Tr. 552:6-16; 811:12-23) Then, because he tended to think in "three dimensions," Dr. Zahler used what are known as "Dreiding models" in order to further develop

his idea and to see if "what [he] had in [his] mind was somehow evident in that physical model." (Tr. 552:12-16; 796:2-22; 811:17-812:11; PDX 531) The use of these models caused Dr. Zahler to solidify his thinking as to the structure of entecavir and to determine that it may be a "useful structure" because entecavir overlapped "quite nicely" with the Dreiding model for 2'-deoxyguanosine (with the exception of the exocyclic methylene group). (Tr. 812:12-813:20)

37. After Dr. Zahler used the Dreiding models to conceive of entecavir, his team then used a proprietary, computer-based computational model in order to better predict entecavir's preferred conformations (or preferred shapes), the purpose of which was to see if entecavir's conformation was similar to those compounds that had antiviral properties, including lobucavir. (Tr. 553:1-554:16; 559:1-10; 562:9-18; 651:20-652:19; 804:9–811:8; 812:12-813:24; PTX 622.0007–09) In 1989, using computer-based molecular modeling in the drug discovery process was an approach that was "unheard of" at the time in nucleoside drug discovery programs. (Tr. 806:13–807:1; 810:23–811:8) Thus, Dr. Zahler did not invent entecavir utilizing one of the three general drug discovery approaches. (Tr. 1141:6–11)

38. At this point in the process of discovering entecavir, in Dr. Zahler's mind, the factor that distinguished entecavir from 2'-deoxyguanosine was the addition of the exocyclic methylene group to the five-membered ring. (Tr. 812:18-23; 815:13-16) However, Dr. Zahler had concern about what the impact would be of adding the exocyclic methylene group to the natural nucleoside. (Tr. 814:1-815:16) Dr. Zahler therefore had members of his team, including Dr. Joseph Tino and Dr. Val Goodfellow, perform the computer modeling discussed above; this modeling process demonstrated that entecavir did indeed "overlap nicely" with 2'-

deoxyguanosine, which motivated Dr. Zahler to attempt to make (or synthesize) entecavir. (Tr. 553:14-555:4; 816:23-817:10; 969:14-19)

39. In performing this computer modeling in May 1990, Dr. Zahler's team selected several different compounds to compare to entecavir via computer modeling and to help "validate" the computer model. (Tr. 559:1-561:11; 563:3-564:3; 573:4-9; 658:3-9; 969:20-970:14) The compounds used in this process included lobucavir, the natural nucleoside 2'-deoxyguanosine, and another carbocyclic nucleoside analog of 2'-deoxyguanosine ("2'-CDG" or "CDG"). (Tr. 559:11- 561:11; 654:7-655:7; 670:23-671:22; 975:15-18) The only two compounds used in this computer modeling and validation process that were not compounds originally synthesized at BMS were (1) 2'-deoxyguanosine; and (2) 2'-CDG. (Tr. 560:14-18; 658:10-15) 2'-CDG was chosen for use in this process as a "positive control," in that it had shown antiviral activity. (Tr. 564:4-13; 569:22-570:4) As BMS continued this modeling process, they refined the model; eventually the results showed that both entecavir and 2'-CDG demonstrated similar conformations to lobucavir, and that entecavir might have similar antiviral properties to lobucavir. (Tr. 658:19-660:20) Dr. Zahler was aware of these testing procedures and results, as he was "heavily involved" in this testing process. (Tr. 660:21-24)

40. Once the computer modeling showed that entecavir could have promising antiviral properties, Dr. Zahler's team set out to synthesize entecavir. (Tr. 817:2-818:8) Dr. Zahler went to Dr. Slusarchyk with his conception, and Dr. Slusarchyk (along with an associate of his at BMS) began the synthesization process. (Tr. 503:10–24) Dr. Slusarchyk, as he explained a good chemist would, "had [] a very good idea" of how to synthesize entecavir right away. (Tr. 503:10–506:20) Nevertheless, according to Dr. Zahler, the synthesis of entecavir was

not an easy process, as the compound turned out to be harder to make than Dr. Zahler would have thought. (Tr. 818:4-8) After six months, Dr. Slusarchyk and his associate at BMS were able to synthesize entecavir. (Tr. 822:11-823:15; 912:6–17)

41. Shortly thereafter, entecavir was tested for antiviral activity. (Tr. 827:12-14) Those test results showed that entecavir had modest but real activity against HSV-1, HSV-2 and VZV. (Tr. 828:1-5) Entecavir's activity against HSV-1 was fourfold less than that of acyclovir, the standard in the field. (Tr. 828:1-5; 829:2-4) Entecavir was not tested against hepatitis B, because BMS did not have a hepatitis B assay at the time. (Tr. 828:6-15) Due to its modest initial test results for herpes activity and against VZV, BMS did not take steps to further develop entecavir; instead, the compound was "put on the shelf" at BMS for a number of years. (Tr. 828:16-829:1)

C. The Person of Ordinary Skill in the Art to Which the '244 Patent Is Directed

42. Teva's expert, Dr. Heathcock, defined a person of ordinary skill in the art to which the '244 Patent is directed as "a medicinal chemist" who has a Ph.D. in organic chemistry or in medicinal chemistry (though Dr. Heathcock said that the former is more likely than the latter). (Tr. 151:22–152:6; 152:20–153:1) According to Dr. Heathcock, the person of ordinary skill has been working for two or three years as a medicinal chemist, and can apply the tools of organic chemistry to design and make compounds. (Tr. 152:7–153:9) Alternatively, the person of ordinary skill has a bachelor's degree or master's degree in organic or medicinal chemistry and has been working in the field for 10–15 years. (Tr. 153:13–19; DDX 47)

43. While BMS's expert, Dr. Schneller, testified at trial that the person of ordinary

skill in the art would "be defined a little differently" than the person defined by Dr. Heathcock, Dr. Schneller did not testify at trial as to the nature of these specific credentials. (Tr. 1139:3–13) In his expert report, Dr. Schneller defined a person of ordinary skill in the art as having "a Ph.D. and at least five years' experience in synthetic organic chemistry and at least three years' experience with nucleoside analogs (including carbocyclic nucleoside analogs), synthetic experience at the bench, familiarity with the work of other nucleoside analog scientists (through reading the literature and/or attendance at meetings), and presentation of papers or posters." (DTX 239.0017 at ¶ 51) At trial, when asked whether it mattered whether the Court utilized his definition of a person of ordinary skill in the art, or that put forward by Dr. Heathcock, Dr. Schneller opined that it did not, as "a person of ordinary skill can be defined in a number of ways," all of which would be "acceptable" to Dr. Schneller. (Tr. 1139:14–20)

44. Dr. Heathcock stated that Dr. Schneller's position as to the level of the person of ordinary skill in the relevant art is a person of "more than ordinary skill." (Tr. 153:24–154:14) Dr. Heathcock disagreed with Dr. Schneller's view that a person of ordinary skill would have some experience with nucleoside analogs because "medicinal chemists are quite versatile." (Tr. 154:15-17) Citing specific examples of medicinal chemists he had encountered as a consultant throughout the years, Dr. Heathcock explained that such chemists can move among projects in various therapeutic areas with ease, and do not "need to work three years [in a particular therapeutic area within medicinal chemistry] before they could begin to be considered ordinary." (Tr. 154:15–156:9)

45. Both Dr. Heathcock and Dr. Schneller stated that regardless of which definition of

the person of ordinary skill in the art is found to be correct, their opinions as to the validity of the patent would remain the same. (Tr. 157:14–158:5; 1139:3–1140:1)

46. In its opening post-trial brief, BMS appears to adopt Dr. Heathcock's definition of a person of ordinary skill in the relevant art, stating that in 1985, when Dr. Zahler began working on nucleoside analogs at BMS, he "had the exact credentials possessed by a person of ordinary skill in the art: a Ph.D. in chemistry, a few years of experience in medicinal chemistry, *and no experience with nucleoside analogs*." (D.I. 150 at ¶ 8) (emphasis added)

47. Accordingly, the Court adopts Teva's definition of the person of ordinary skill in the art.

D. Nucleoside Analogs and the Scope and Content of Prior Art References Relating to Nucleoside Analogs

48. BMS's and Teva's experts, as well as Dr. Zahler, all identified three classes of nucleoside analogs that were in existence at the time of entecavir's invention: nucleoside analogs with a furanose (or carbohydrate) ring (also called "furanosides"), acyclic nucleoside analogs (also called "acyclics"), and carbocyclic nucleoside analogs (also called "carbocyclics"). (Tr. 158:11–160:1; 767:5–769:4; 1111:24–1112:7; D.I. 150 at ¶ 23; PDX 58-1; DDX 48)

1. Furanosides

49. In 1959, a furanoside known as cytosine arabinoside ("Ara-C") was developed and was ultimately approved by the FDA as an anticancer agent. (Tr. 160:2–161:4; DDX 49) In 1960, a nucleoside analog in this category known as adenine arabinoside ("Ara-A") was developed and eventually approved by the FDA as an antiviral agent to treat the herpes virus. (Tr. 161:5–15; 176:7–14; DDX 49)

50. Furanosides are straightforward to synthesize. (Tr. 773:23–24; 1115:6–9)

51. Furanosides were a "fairly well developed field" at the time of entecavir's invention (and prior to it), having been the focus of the previous twenty-five years of research. (Tr. 773:23–774:2)

2. Acyclics

52. The "classic example" of an acyclic nucleoside analog is acyclovir, which was discovered in 1977, (JTX 66.001), and eventually became approved by the FDA to treat the herpes virus. (Tr. 162:9–13) Acyclovir is an analog of the natural nucleoside 2' deoxyguanosine. (Tr. 161:21–162:9; DDX 51) In 1988, the developers of acyclovir were awarded the Nobel Prize. (Tr. 1113:5–12)

53. There were additional acyclic nucleoside analogs in the prior art. (Tr. 162:19–163:4) One paper reported "several dozen" such compounds. (Tr. 163:1–2) These compounds generally all contained a guanine ring, and their differences could be found on the sugar portion of the compound because it was "not very difficult" to make changes to the "side chain." (Tr. 163:2–20) Thus, acyclics are easy to make. (Tr. 773:22–23; 774:3–4; 1114:16–19)

54. Many acyclics showed antiviral activity. (Tr. 164:2–3) Accordingly, several acyclic compounds were put into clinical development. (Tr. 164:2–5)

55. Ganciclovir is another example of an acyclic nucleoside analog. (Tr. 772:22–24; 1112:13–24) Ganciclovir was active against the herpes virus and was on its way to being FDA approved at the time of entecavir's invention. (Tr. 772:8–10; 1112:19–1113:3)

56. At the time of entecavir's invention, acyclics were "a crowded field," as many

scientists had worked with acyclics and made many such compounds. (Tr. 168:13–20) Even so, there were plenty of researchers who were still using acyclic nucleoside analogs as lead compounds during this time. (*See, e.g.*, JTX 87.0001; Tr. 284:17–287:1)

3. Carbocyclics and 2'-CDG

a. Use of Carbocyclics in the Late 1980s and Early 1990s

57. A carbocyclic is an analog that has a base portion, and a sugar/carbohydrate portion with a carbon atom instead of an oxygen atom at the 5 prime position. (Tr. 165:8–11; DDX 53)

58. One example of a carbocyclic that existed in the prior art is aristeromycin, which is an analog of the nucleoside adenosine. (Tr. 164:24–165:12) Aristeromycin was first synthesized in 1966 by Dr. Y. Fulmer Shealy and a group of researchers with whom Dr. Shealy worked. (Tr. 165:11–16; DTX 41) The base portion of aristeromycin is an adenosine ring and the sugar portion (also known as the furanose ring) has a carbon instead of an oxygen at the 5 prime position. (Tr. 165:1–12; DDX 53)

59. While a few compounds in the other above categories had been FDA approved at the time of entecavir's invention, no carbocyclics had been FDA approved. (Tr. 1114:1–3)

60. Carbocyclics take a long time to synthesize. (Tr. 1114:7–13) Despite this, chemists were, in fact, regularly synthesizing carbocyclics in the late 1980s and the beginning of the 1990s. For example, even BMS's expert, Dr. Schneller, who testified as to the difficulty in synthesizing carbocyclics, oversaw students in his laboratory synthesizing carbocyclics during this time period, and noted that "it was most of what we did." (Tr. 1071:15–1072:7; 1183:8–12; 1194:4-11) Dr. Schneller also confirmed that other groups including researchers at the Southern

Research Institute ("SRI"), Glaxo Group Research Ltd. ("Glaxo"), Syntex Research ("Syntex"), and even BMS itself were synthesizing carbocyclic nucleosides during the relevant time period, in spite of the difficulty of this process. (Tr. 1194:8–1195:8)

61. Accordingly, in the late 1980s, the ordinary medicinal chemist would and did explore the field of carbocyclic nucleosides in attempting to develop antiviral drugs. As Teva's expert Dr. Heathcock explained, carbocyclics was a group "that people would notice as a . . . fertile place to go to look for a new drug." (Tr. 168:20–169:7) By this time, the areas of furanosides and acyclics were crowded, (Tr. 168:13–20; 773:23–774:2), while the area of carbocyclic nucleoside analogs was "a fertile field that hadn't been plowed very much yet." (Tr. 168:20–24) Dr. Schneller, for his part, confirmed on cross-examination that by the 1980s, there was a growing interest in the area of carbocyclic nucleoside analogs, in part due to the work that Dr. Shealy and SRI were doing with those analogs. (Tr. 1154:5–1155:10)

62. A 1986 article by Victor E. Marquez & Mu-Ill Lim entitled "Carbocyclic Nucleosides" ("Marquez"), published in *Medical Research Reviews*, notes generally that carbocyclic nucleosides "are endowed with an interesting range of biological activities, especially in the areas of antiviral and anticancer chemotherapy," and concludes that "good antiviral activity appeared to be the rule rather than the exception among carbocyclic nucleosides." (*Id.* at 171.0004, 171.0038)

63. An article by researchers at Glaxo in the U.K. including Keith Biggadike ("Biggadike" or the "Biggadike article") was published in 1987. (DTX 150) The article, *inter alia*, stated that "[t]here is considerable current interest in the synthesis of carbocyclic nucleosides in our laboratories and elsewhere [citing to the work of Dr. Shealy and others] due to

the high levels of selective antiviral activity displayed by some members of this group [citing in part to a 1984 article by Dr. Shealy that is more fully discussed below]." (*Id.*)

64. An article by G.V. Bindu Madhavan ("Madhavan" or the "Madhavan reference") and others with Syntex published in the *Journal of Medicinal Chemistry* in 1988 revealed that the researchers at Syntex were developing carbocyclic nucleoside analogs and analyzing the antiviral activity of such analogs. (JTX 81; 1194:12- 1195:8)

65. And BMS itself was working in the carbocyclics field in the late 1980s, having invented lobucavir prior to the invention of entecavir. (Tr. 883:12–884:13; 887:3–6) In September 1989, at a scientific conference, Dr. Zahler and others at BMS reported on the promise of lobucavir (referred to as "SQ-33054") as a "novel, synthetic nucleoside analog with excellent activity" against HSV-1 and HSV-2, human cytomegalovirus, and VZV. (PTX 443.0003; Tr. 894:14–20; 1156:14–20) In fact, the testing results that the BMS group obtained on lobucavir proved it to be "superior to acyclovir, and comparable to ganciclovir" against the above viruses. (Tr. 896:9–17; PTX 445.0003)

66. Two other groups, Abbott Laboratories and Nippon Kayaku, had also independently developed the carbocyclic analog that BMS called lobucavir. (Tr. 884:10–885:24; 887:22–888:12; PTX 622.0006)

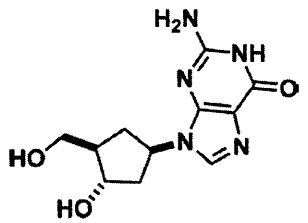
67. An article summarizing the antiviral research to date by Dr. J.A. Montgomery of SRI was published in October 1989 ("Montgomery 1989"). (DTX 172.0003–04) Dr. Montgomery concluded that of the compounds identified by SRI with promising antiviral activity, "[b]y far the most active and selective agents are carbocyclic nucleoside analogs . . . ." (DTX 172.0004; Tr. 189:3–12) Dr. Heathcock noted that such a statement by a "very well

regarded" chemist served as a "pretty open invitation . . . to medicinal chemists to look at that class of compounds as leads." (Tr. 188:19; 189:3–15)

b. 2'-CDG

68. Another carbocyclic nucleoside analog that existed and was described in the prior art at the time of entecavir's invention was 2'-CDG. (Tr. 166:21–167:15; 531:1–6) Indeed, Dr. Zahler was aware of 2'-CDG and the work that chemists at SRI had done with the compound before he began his development of entecavir. (Tr. 531:6–22) In that regard, as is discussed more fully below, 2'-CDG was cited as prior art in applications for other patents on which Dr. Zahler was listed as an inventor, including patent applications filed in December 1988 and July 1990 (before the first application for the '244 Patent was filed in October 1990). (Tr. 622:2–627:19; JTX 103; DTX 163)

69. Dr. Shealy of SRI invented 2'-CDG in 1984. (Tr. 168:24–169:4; DTX 126) 2'-CDG is a carbocyclic nucleoside analog of the natural nucleoside 2' deoxyguanosine. (Tr. 167:1–11; 533:5–12; DDX 54) 2'-CDG mimics the natural nucleoside 2' deoxyguanosine in that the compounds have identical bases, but the sugar/carbohydrate portion of 2'-CDG has a carbon atom at the 5 prime position, instead of an oxygen atom. (Tr. 167:1–8; 533:5–12; DDX 54) 2'-CDG can be depicted as follows:



(D.I. 151 at ¶ 45)

70. 2'-CDG was singled out as a promising compound in the carbocyclics field, (Tr. 171:19–173:18), in that it demonstrated "very good" antiherpes activity. (Tr. 168:24–169:3; 173:20–174:1)

71. For example, Dr. Shealy's synthesis of 2'-CDG was published in a six-page article in the *Journal of Medicinal Chemistry* in 1984: "Synthesis and Antiviral Activity of Carbocyclic Analogues of 2'-Deoxyribofuranosides of 2-Amino-6-substituted-Purines and of 2-Amino-6-Substituted-8-Azapurines" ("Shealy 1984").[8] (Tr. 172:1–172:19; DTX 126)

72. Shealy 1984 discusses testing results regarding a number of carbocyclic analogs of nucleosides, including 2'-CDG. (DTX 126.0001) The article reported that 2'-CDG showed better activity in *in vitro* testing against the herpes virus (both HSV-1 and HSV-2) than did Ara-A, the FDA-approved drug in the furanoside family used to treat the herpes virus. (Tr. 174:2–176:1; 176:15–22; DTX 126.0002) The article went on to note that "[i]n these tests vs. HSV-1, the carbocyclic analog[] of 2'-deoxyguanosine (12) [along with three other compounds] were the most potent compounds . . . . The carbocyclic analog of 2'-deoxyguanosine (12) showed excellent activity (VR, 3.7) and high potency (MIC50, .0.8 mcg/mL) against strain MS of HSV-2." (DTX 126.0002)

73. Dr. Shealy obtained a U.S. Patent No. 4,543,255 entitled "Carbocyclic Analogs of Purine 2'-Deoxyribofuranosides" for 2'-CDG and a family of related compounds, which issued and was published in September 1985 ("Shealy '255 Patent"). (Tr. 177:17–24; DTX 151) The Shealy '255 Patent discloses the invention of a number of compounds, including

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[8] 2'-CDG is referred to as "compound number 12" in Shealy 1984. (D.I. 151 at ¶ 19)

2'-CDG, that are carbocyclic analogs of purine 2'-deoxyribofuranosides, explaining that these compounds are useful in the treatment of viral infections. (DTX 151) The patent describes 2'-CDG as one of two compounds that was "markedly more effective than was [the FDA approved drug] Ara-A." (Tr. 178:13–18; DTX 151.0008)

74. 2'-CDG is also one of a number of carbocyclic nucleosides referenced in the Marquez article; it is referred to in the article twice, and neither time by name. Instead, in one instance, a tautomer (a type of structural isomer) of 2'-CDG appears as an entry (entry number 37d) in a table of a large number of different carbocyclic purine nucleosides. (DTX 171.0010) In the other instance, in the third paragraph of Section III.A.b. of the article, 2'-CDG is referenced by entry number (along with other compounds). The reference notes, citing to Shealy 1984, that 2'-CDG showed activity against HSV-1 and demonstrated that it was more potent against HSV-2 than certain other carbocyclic nucleosides. (DTX 171.0017-18 (referencing 2'-CDG in group of nucleoside analogs listed as entry numbers "37c-f"))

75. Another Shealy article, a five-page 1987 article in the *Journal of Medicinal Chemistry*, was titled "Synthesis and Antiviral Evaluation of Carbocyclic Analogues of 2-Amino-6-substituted-purine 3'-Deoxyribofuranosides" ("Shealy 1987"). The article focuses on the synthesis and antiviral properties of carbocyclic analogs of 2-amino-6-substituted-purine 3'-dexoyribofuranosides. (DTX 125) While Shealy 1987 is, therefore, not an article primarily about 2'-CDG, as part of its discussion of these other carbocyclic analogs, the article discloses that 2'-CDG showed *in vivo* activity against both HSV-1 and HSV-2. (Tr. 181:13–182:3; DTX 125.0002)

76. Additional testing was conducted on 2'-CDG in the 1980s. 2'-CDG is a chiral

compound, meaning there are two different ways to arrange the atoms of the compound and achieve the same overall connectivity. (Tr. 183:6-12; DDX 55) These two different forms are called enantiomers; they are non-superimposable mirror images of one another. (Tr. 182:15-24; 183:14–18) In drug compounds that are chiral, generally only one of the two enantiomers are responsible for the drug's biological activity. (Tr. 184:3–5) Dr. Shealy and other researchers at SRI did additional work on 2'-CDG to determine which enantiomer triggered its biological activity. (Tr. 185:12–186:5; DTX 173) Their testing proved that the enantiomer of 2'-CDG responsible for its activity is that corresponding to the natural nucleoside, 2'-deoxyguanosine. (Tr. 185:23–186:14; DTX 173)

77. Other researchers outside of SRI engaged in additional testing of 2'-CDG. (*See, e.g.*, DTX 152) Peter M. Price and other researchers with the Mount Sinai School of Medicine published the results of testing of 2'-CDG against the hepatitis B virus in an November 1989 article (the "Price article"). (*Id.*) Price reported that 2'-CDG showed excellent activity against the hepatitis B ("HBV") virus. (Tr. 186:22–187:10; DTX 152 ("Treatment of 2.2.15 cells (10) with as little as 25 ng of 2'-CDG per ml resulted in the almost complete disappearance of replicating HBV . . . .")) The group's testing also demonstrated that 2'-CDG "was nontoxic in concentrations up to 200 times the minimum effective inhibitory concentration." (DTX 152; Tr. 187:16–19) According to Dr. Heathcock, Price's testing demonstrated that 2'-CDG "had a very good therapeutic window [because] [i]t was effective at a level, much lower than its toxic level." (Tr. 187:21–24)

E. Selection of 2'-CDG as a Lead Compound

78. As noted above, the earliest priority date for the '244 Patent is October 18, 1990.

(JTX 1; Uncontested Facts at ¶¶ 3, 6) As of this time frame, 2'-CDG would have been chosen as a lead compound by the person of ordinary skill in the art; indeed, researchers at other companies actually utilized 2'-CDG as a lead compound. (Tr. 191:11–20)

79. Dr. Heathcock testified that 2'-CDG would have been noticed and recognized as "a very good lead compound" during the relevant time frame. (Tr. 199:8–11) In support of this opinion, Dr. Heathcock cited to the facts that (1) 2'-CDG is structurally related to the natural nucleoside deoxyguanosine, only differing by the change from one oxygen atom into a carbon atom on the five-membered ring; (2) it showed excellent activity against the herpes virus and had *in vivo* potency; and (3) it had actually been selected as a lead compound by researchers. (Tr. 199:8–24; 200:15–21)

80. In his 1989 article that identified carbocyclics as "the most active and selective" of the antiviral compounds, Dr. Montgomery singled out 2'-CDG as a promising compound in the carbocyclics field: "By far the most promising carbocyclic purine nucleosides for the treatment of herpes infections are in the 2'-deoxyribo series . . . (Shealy et al., 1984b). Of these the most likely compounds appear to be the 2'-deoxyguanosine analog (CDG, 32) and its prodrug forms." (DTX 172.0014; Tr. 190:7–15) Further, Dr. Montgomery stated that 2'-CDG was "five to six times as potent as acyclovir against" HSV-1 and HSV-2 "in plaque reduction assays in human foreskin fibroblasts." (Tr. 1181:10–15; DTX 172.0016) Thus, the Montgomery 1989 article was a "lamp post that really illuminate[d] 2'-CDG as [] a very exciting lead compound to work from." (Tr. 191:5–10)

81. The testimony of BMS's own expert, Dr. Schneller, supports the conclusion

that 2'-CDG would have been (and was) chosen as a lead compound in this time period. In his trial testimony, upon direct examination, Dr. Schneller first stated that 2'-CDG was "on the list" (along with hundreds of other compounds) as a possible lead compound for antiviral drug research. (Tr. 1111:1–16; 1113:13–17) On cross-examination, however, Dr. Schneller agreed that the Glaxo researchers had considered 2'-CDG to be a lead compound. (Tr. 1175:21–1176:6; 1210:13–23) He also agreed that researchers at SRI had treated 2'-CDG as a promising compound. (Tr. 1181:16–20) Furthermore, Dr. Schneller conceded that he did not "completely disagree" with Dr. Heathcock's opinion that 2'-CDG would have been and was used as a lead compound, (Tr. 1164:15–19), and clearly acknowledged that in the relevant time period other "talented" chemists did in fact treat 2'-CDG as a lead compound. (Tr. 1166:3–15; 1167:4–10)

82. As noted above, some of those other chemists include the group led by Keith Biggadike at Glaxo. Biggadike and other researchers at Glaxo published the 1987 Biggadike article that described their synthesis of 2'-CDG. (Tr. 191:18–192:18; DTX 150) The article notes that their interest in the compound was triggered by the "high levels of selective antiviral activity" displayed by 2'-CDG (as well as other members of the carbocyclics family). (Tr. 192:19–193:4; DTX 150) The fact that Glaxo invested efforts to make 2'-CDG is, as Dr. Heathcock put it, "evidence that Glaxo had selected CDG as a lead structure to work from." (Tr. 194:3–10)

83. Indeed, in 1988, Glaxo researchers (led by Alan D. Borthwick, and including Keith Biggadike), published an article (the "Borthwick article") reporting that they had made a compound identical to 2'-CDG but with one addition: they attached a fluorine atom to the carbon atom at the 2 prime position of the sugar portion. (Tr. 194:13–195:10; 1214:11–1215:14; DTX

170–170.0002; DDX 56) The researchers reported that the compound that they created had good potency against HSV-1 and HSV-2. (Tr. 195:12–14; DTX 170) In fact, the new compound was found to be approximately thirty times more active than acyclovir—a drug FDA-approved to treat herpes at the time—against HSV-1. (Tr. 195:18–196:1; DTX 170) The new compound also showed "extremely high levels of activity" against HSV-2. (DTX 170; Tr. 196:19–21) This group's synthesis of an analog of 2'-CDG demonstrates that the chemists "took the clues from probably the Shealy papers . . . and they selected 2'-CDG as their lead compound. They made an analog and it was active . . . even more active than acyclovir." (Tr. 197:23–198:3; *accord* 273:13–20; 1216:10–20) In other words, the Borthwick group "took [2'-CDG] and improved it by adding the fluorine." (Tr. 276:22–24) On cross-examination at trial, Dr. Schneller agreed that this article is evidence that "people of skill in the art looked at 2'-CDG and made changes to the sugar portion"—and thus is evidence that people were using 2'-CDG as a lead compound, a starting point, at the relevant time. (Tr. 1213:19–24; 1215:9-11; 1216:10-18)

84. Dr. Schneller himself wrote an article that discussed 2'-CDG: "(±)-Carbocyclic 5'-Nor-2'-deoxyguanosine and Related Purine Derivatives: Synthesis and Antiviral Properties," published in the *Journal of Medicinal Chemistry* in June 1992. (DTX 178; Tr. 1182:14–1183:7) The article states that the authors prepared "derivatives" of, among other compounds, "carbocyclic 2'-deoxyguanosine." (DTX 178.0003; Tr. 1185:1–10) The article further states that "[r]acemic and D-carbocyclic 2'-deoxyguanosine [2'-CDG] (represented as [compound] 1) have shown significant antiviral activity as a result of selective conversion to their 5'-triphosphate derivatives," citing to, *inter alia*, Shealy 1984. (DTX 178.0003; Tr. 1189:20–1191:11) Dr. Schneller disputes that the article's use of the term "derivative[]" means that he used 2'-CDG as a

lead compound, noting that he may have "misspoken" in using the term "derivative" in the article. (Tr. 1185:11–20) However, it is at the very least clear that Dr. Schneller had read about Shealy's invention of 2'-CDG, noted that 2'-CDG had shown significant antiviral activity, and wrote about 2'-CDG while synthesizing carbocyclics and investigating their antiviral activity. (DTX 178.0003; Tr. 1189:17–1193:8)

85. Even considering the track records of acyclics and furanosides, 2'-CDG could easily have been viewed by a person of skill in the art as a more promising lead compound than compounds in those classes, because researchers were reporting during the relevant time that 2'-CDG showed better antiviral activity than both Ara-A, an FDA-approved furanoside, (Tr. 174:2–176:1; 176:15–22; 178:13–18; DTX 126.0002), and acyclovir, an FDA-approved acyclic. (Tr. 1181:10–15; DTX 172.0016)

86. An later article published in *Current Pharmaceutical Design* in April 1997 (the "Mansour and Storer article") appears to confirm that 2'-CDG was used in the past in the role of a lead compound, stating that "[t]he carbocyclic analogue of 2'-deoxyguanosine . . . has played a pivotal role in providing a template for the development of carbocyclic nucleoside analogue programmes." (DTX 154.0017) Dr. Schneller agreed that this description "sounds like [the authors] think . . . 2'-CDG was a lead compound," noting that "[t]hat's what [the authors] say" in the article. (Tr. 1245:23–1246:1)

87. Any toxicity then-associated with 2'-CDG as of October 1990 would not have deterred the person of ordinary skill in the art from selecting 2'-CDG as a lead compound, because at that time, 2'-CDG was not then known (as it would later come to be known) as being associated with a high toxicity. (DTX 126.0002; DTX 172.0014; DTX 152.0001)

88. For example, the Shealy 1984 article did not provide clear indication that 2'-CDG was toxic. Table III of the article contains anticancer data, including references to the results of testing as to the relative toxicity of a number of compounds, including 2'-CDG (referenced in the table as compound 12), which results were reported on day five of a nine-day trial. (DTX 126.003; Tr. 266:3-8) A footnote in that table explains that a "dose is considered to be toxic (t) if T/C < 85% or the weight-change differential is greater in magnitude than -4g." (DTX 126.003, tbl.III & n.d) However, by that criteria, the data listed in Table III did not suggest that 2'-CDG was toxic, as to the dosage reported for 2'-CDG (100 milligrams per kilogram per day). (DTX 126.0003; Tr. 375:22–378:3) Dr. Heathcock testified on cross examination that one possible interpretation of this data for 2'-CDG—had its test results been reported on day nine of the trial or were they based on a dosage of 200 milligrams per day—was that the authors of the article would have had to report toxicity issues. (Tr. 267:12-23) However, Dr. Heathcock also said that this was a "pretty hypothetical" conclusion, and that if the authors believed there were toxicity issues with 2'-CDG, they "would have said something like that in the paper." (*Id.*) Dr. Schneller, for his part, did not opine that the Shealy 1984 article provided any indication that 2'-CDG was toxic.

89. In the 18-page Montgomery 1989 article, there is a table (table 6) on one page of the article that reports on the activity of 2'-CDG (and other compounds) in mice that were infected with HSV-1. (DTX 172.0015) One column (titled "Uninfected toxicity controls (survivors/total)") of that table reports on the number of mice in a control group (a group that were not infected with HSV-1) that survived the testing; the results in this column shows that all of those mice did, in fact, survive. (*Id.*) Another column of the table notes how many virus-

infected mice survived 21 days-worth of testing, and notes that the number of such survivor mice decreased as the dosage of 2'-CDG rose above 2.5 mg/kg/day. (*Id.*) However, nowhere in the table (nor in the article) do the authors cite 2'-CDG as a toxic compound. (*Id.*) Instead, as noted above, on the page of the article just prior to table 6, the authors instead call out 2'-CDG's "promising" anti-herpetic properties. (DTX 172.0014) Dr. Schneller, for his part, did not opine that the Montgomery 1989 article provided any indication that 2'-CDG was toxic.

90. An article by Lee Bennett, Shealy and others at SRI published in 1990 ("the Bennett article") did note that 2'-CDG appeared to have cytotoxic effects. (JTX 90.0007) While the Bennett article also states that "[c]ellular DNA polymerases may also be inhibited to some extent" by 2'-CDG, the article's abstract highlights that "2'-CDG apparently is a good substrate for the virus-coded kinase and a very poor substrate for cellular phosphorylating enzymes." (JTX 90, 90.0007) Dr. Heathcock noted that this discussion about cytotoxicity and 2'-CDG was largely couched in "tentative" terms, and would not automatically steer the ordinary medicinal chemist away from selecting 2'-CDG as a lead compound. (Tr. 257:4–259:4; 259:14–15; JTX 90.0007) Dr. Heathcock explained that the abstract of the Bennett article suggests that 2'-CDG has a "greater effect on the virus than . . . on the cell itself," which would be interpreted to mean that 2'-CDG "would not be especially toxic" because it "influenc[es] the cell more than it influences the virus." (Tr. 373:9–374:18) While the Bennett article was accepted for publication on March 13, 1990, and was published at some point in 1990, it is not clear from the record as to whether it was published prior to October 18, 1990. (JTX 90.0001; Tr. 256:14-19; 371:16-372:12)

91. While Dr. Schneller's expert report opines that 2'-CDG was a less fruitful lead

than other carbocyclics because it "came to be understood as cytotoxic," two supporting citations for this proposition come from 1992 (after the October 1990 priority date regarding the patent). (DTX 239.0013 & n.16) The third is the 1990 Bennett article which, as explained above, is tentative in the way it describes the impact of cytotoxicity associated with 2'-CDG. (*Id.*)

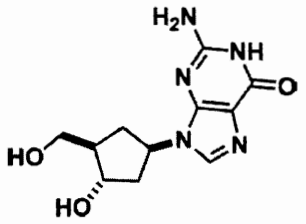
92. Testimony from BMS's own expert, Dr. Bud Tennant, illuminates that the toxicity of 2'-CDG was not well known as of October 1990. Dr. Tennant explained that woodchucks are an animal model used to test potential hepatitis B drugs before they are tested in humans, because the woodchuck hepatitis virus is similar to the human hepatitis B virus. (Tr. 462:10–21) Dr. Tennant tested 2'-CDG on his woodchuck colony to determine the effects of the compound against the woodchuck hepatitis virus. (Tr. 988:22–989:12; JTX 141) This testing occurred in 1990 and 1991. (Tr. 989:21–22; JTX 141) Dr. Tennant was "absolutely not aware" of any toxicity of 2'-CDG before he started the testing and noted that, had such toxicity data been available, he would have considered it. (Tr. 1022:16–1023:6) Had Dr. Tennant known that 2'-CDG was toxic at this time, he would not have done the studies "the way they were done." (Tr. 1022:16–21) Indeed, Dr. Tennant's July 30, 1991 report summarizing his testing (which was never published) characterized the "high fatality rate . . . associated with 2'-CDG treatment" as "unanticipated." (Tr. 1023:7–12; 1027:21–23; JTX 141.0007)

93. As was stated above, the 1989 Price article reported that 2'-CDG "was nontoxic in concentrations up to 200 times the minimum effective inhibitory concentration." (DTX 152; Tr. 187:16–19) And, in a later 1992 article, the authors wrote that "[n]either we nor Shealy et al. (20) found that 2'-CDG was cytotoxic *in vitro* (21) or toxic *in vivo*." (DTX 185.0005)

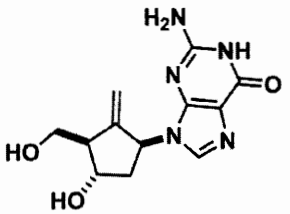
94. Even if some evidence did exist prior to October 1990 indicating that 2'-CDG was associated with toxicity, such evidence was limited, and would not have discouraged the ordinary medicinal chemist from using 2'-CDG as a lead compound. Indeed, Dr. Slusarchyk, the medicinal chemist who designed the synthesis for entecavir, testified that toxicity data about nucleoside analogs that he was making "wouldn't deter [him] from making more compounds in the area to investigate further" as he was a "medicinal chemist," not a "toxicologist." (Tr. 508:8–19)

F. Similarities and Differences Between the Claimed Invention and 2'-CDG

95. The only structural difference between entecavir and 2'-CDG is the addition of one carbon atom at the 5 prime position of the ribose portion of entecavir. (Tr. 211:2–22; 219:19–220:7; DDX 60) 2'-CDG has a single carbon atom at the 5 prime position while entecavir has an exocyclic methylene group (a "carbon-carbon double bond") at the 5 prime position. (Tr. 220:2–7; 1249:13–19; DDX 62) The remaining structural features of entecavir and 2'-CDG are the same (both have a carbocyclic core, a guanine base, a hydroxyl (OH) group at the 3 prime position and a hydroxymethyl (CH_2OH) at the 4 prime position. (Tr. 1247:19–1249:11) As previously illustrated, the compounds 2'-CDG and entecavir can be depicted as follows:



2'-CDG



entecavir

(D.I. 151 at ¶ 45)

96. It is clear, as Dr. Heathcock opined, that the two compounds would have been deemed "structurally very similar" by a person of ordinary skill in the art. (Tr. 219:5-220:8) In his testimony at trial, Dr. Zahler, who "think[s] in three dimensions," characterized the compounds "as both structurally similar and dissimilar." (Tr. 547:6–8; 608:16–19) However, a July 1997 article authored by BMS scientists, including Dr. Zahler, illuminates how BMS viewed entecavir and 2'-CDG well before this litigation. (JTX 107) In a discussion of entecavir's (referred to in the article as "BMS-200475") activity against the hepatitis B virus, the authors state that "2'-CDG, *a structurally similar* guanine-based nucleoside in which the natural furanose oxygen is also replaced by a carbon, has been shown to inhibit hepadnaviral reverse transcription in this fashion." (JTX 107.0003; Tr. 612:5–6; 613:8–18) (emphasis added) In his trial testimony, Dr. Zahler claimed that the words "structurally similar" in the article are used "[l]oosely" and are "not [his] words," yet it is clear that he is listed as an author of this article. (Tr. 614:14–19) Another 1998 article authored by BMS scientists again calls out the structural similarity between 2'-CDG, entecavir and lobucavir (another carbocyclic analog) in their triphosphate forms: "To date, the only truly effective priming inhibitors appear to be BMS-200475-TP [entecavir] and lobucavir-TP . . .and the *structurally related* compound 2'-CDG-TP." (JTX 108.0008) (emphasis added) As Dr. Zahler confirmed, papers authored by BMS chemists prior to this litigation discussed the "activity" of 2'-CDG as well as its "structural similarities" with entecavir. (Tr. 616:14–24; 617:10–13) These papers did not, on the other hand, discuss "structural differences" between the two compounds. (Tr. 617:1–9)

97. As was previously noted above, under Dr. Zahler's direction, BMS engaged in

computer modeling of nucleoside analogs in three dimensions—entering data into the computer about a compound to determine its three dimensional shape (i.e., its conformation). (Tr. 553:4–554:22) Through this computer modeling, Dr. Zahler and his team confirmed that entecavir and 2'-CDG should have similar antiviral activity. (DTX 120.0001) Specifically, BMS plotted three-dimensional conformations of nucleoside analogs, and identified a boundary (that resembled a "Pac-Man" shape) showing which of those conformations would be "expect[ed] to have activity." (DTX 120.0001; Tr. 565:6-566:4; 656:24-657:9) Both entecavir and 2'-CDG were within that boundary. (Tr. 566:11-567:3; 658:16-659:11; DTX 120.0001) Thus, both entecavir and 2'-CDG had similar three dimensional conformations because both conformations were in the boundary that BMS used to predict bioactivity. (Tr. 659:12-660:18)

98. While it is true that entecavir's exocyclic methylene group "affects the three-dimensional structure" of the compound, giving it a less flexible carbocyclic ring than 2'-CDG, (Tr. 1080:3–1082:23), Dr. Zahler pointed out that many chemists do not analyze structural similarity between compounds by thinking in three dimensions. (Tr. 886:13–19) Indeed, although the '244 Patent applicants presented Madhavan compound 30 to the PTO as the closest prior art, Dr. Zahler did not know the three dimensional structure of that compound at the time. (Tr. 632:20–633:7) The ordinary medicinal chemist working during the relevant time period to develop an antiviral compound would be primarily focused on two-dimensional structural similarities and differences between compounds while not necessarily thinking of the compounds in terms of their three dimensional conformations.

99. The most significant difference between 2'-CDG and entecavir is that the former

is toxic while the latter is not (Tr. 252:8–13), although this difference was not clear as of October 1990, as explained above.

G. The Substitution of an Exocyclic Methylene Group on the 5 Prime Position of 2'-CDG

100. After selecting 2'-CDG as a lead compound, an ordinary medicinal chemist would have proceeded to make small, conservative changes to 2'-CDG. (Tr. 200:22–201:12; 1146:14–1148:5; 1196:9–14)

101. The ordinary medicinal chemist would have been motivated to make such changes to the carbocyclic portion of 2'-CDG (as opposed to the guanine base) in the relevant time period. For one thing, others were already making similar substitutions during the relevant time period, and were seeing these changes result in antiviral activity. (Tr. 1212:15–19; 1213:19–24; 1215:9–1216:18) Researchers were experimenting with making changes to the guanine base of nucleoside analogs as well. (Tr. 284:17–285:15; 286:10–14; JTX 87) However, Dr. Heathcock explained that the literature showed that modifications to the guanine portion of acyclovir, for example, resulted in "a substantial loss of antiviral potency," such that even the most active of the resulting compounds "were at least 10-fold less active than the guanine derivative." (Tr. 203:6–204:9; JTX 87.0001) Dr. Slusarchyk testified that when synthesizing analogs, it was his practice to make the guanine portions first because other compounds that he was aware of at the time that were active antivirals had the guanine portion. (Tr. 507:13–508:7)

102. According to Dr. Heathcock, the obvious positions to make substitutions on 2'-CDG were at the 2 prime and 5 prime positions of the carbocyclic ring. (Tr. 201:18–202:10; DDX 58) These are obvious locations because they do not implicate the parts of the compound

(such as the guanine base, the hydroxyl and hydroxymethyl groups) that "the biological machinery is probably recognizing." (Tr. 201:20–202:4) Moreover, there are only hydrogen atoms attached at the 2 prime and 5 prime positions, and so a modification at those positions would be a small first step to make. (Tr. 202:5–10)

103. If an ordinary medicinal chemist was to make a small modification to 2'-CDG, that chemist would have looked to do so by examining the smallest elements in the periodic table. (Tr. 204:10–17; JTX 75.0003) Dr. Heathcock testified that the smallest elements are found in the top row of the periodic table; such elements, excluding hydrogen and helium, "have the smallest surface area and they make the short[est] test bonds when they're joined to something else." (Tr. 205:9–16; JTX 75.0003) BMS's expert Dr. Schneller agreed with this point. (Tr. 1196:22–1198:3) Both Dr. Heathcock and Dr. Schneller also agreed that of the elements in this top row of the periodic table, the ordinary medicinal chemist would have avoided lithium, beryllium, boron and neon, as those elements are either toxic, too reactive, or do not react at all. (Tr. 205:22–206:4; 206:14–18; 1198:17–1199:6) This leaves nitrogen, oxygen, carbon and fluorine, but the chemist would probably not have selected either nitrogen or oxygen as a first, conservative change because these elements "would change the physical properties a lot." (Tr. 206:5–10) Accordingly, the chemist would focus on carbon or fluorine because "they would not change the physical properties as much" and "[t]hey would be expected to give stable compounds that aren't much bigger than what you're starting with." (Tr. 206:8–12)

104. As to these two elements, Dr. Schneller identified carbon as "the most conservative" change—"the only one that stuck out" to him. (Tr. 1200:1–1203:6; *accord* 1206:5–11)

105. When starting with 2'-CDG as a lead compound, and making an obvious, conservative substitution to the five-membered ring, using either carbon or fluorine at the 2 prime or 5 prime positions, there are six resulting compounds that a medicinal chemist would have first thought to make. (Tr. 206:19–210:23; DDX 59)

106. The chemist could have added a fluorine at the 5 prime position pointing up or pointing down. (Tr. 207:8–11; DDX 59) The chemist could also have added a fluorine at the 2 prime position pointing up or pointing down, although Glaxo had already made an analog of 2'-CDG with a fluorine added at the 2 prime position pointing up. (Tr. 207:12–18; 1214:4–1215:14; DDX 56, 59; DTX 170–170.0002)

107. Turning to carbon, the chemist would first think to add an exocyclic methylene group (a carbon-carbon double bond) at either the 2 prime or 5 prime positions. (Tr. 207:19–208:1; DDX 59) Dr. Heathcock explained that the chemist would think to join the carbon with a double bond instead of a single bond because an exocyclic methylene group is "a lot shorter" than a single bond, and therefore would "increase[] the surface area and volume of the molecule the least." (Tr. 208:3–11) Dr. Schneller agrees that an exocyclic methylene group is "the shortest bond," characterizing this as a "well-known" concept. (Tr. 1206:20–1207:6)

108. Dr. Schneller considers adding a methyl group (one carbon atom bonded to three hydrogen atoms) onto the five-membered ring of 2'-CDG to be "a conservative change." (Tr. 1208:10–1209:24; DDX 106) Dr. Heathcock agrees that a medicinal chemist might consider this substitution, but it would be a second tier choice because a methyl group is "a little bit bigger" (it adds two hydrogens in addition to the carbon) and has "a little bit longer bond" than the carbon-carbon double bond of the exocyclic methylene group. (Tr. 208:12–209:1; 209:7–13) As

indicated above, the carbon-carbon double bond is shorter than the methyl group. (Tr. 208:3–11; 1204:15–18; 1206:23–1207:4) Thus, substituting a methyl group instead of an exocyclic methylene group would be a bigger change, in that it would increase "the surface area and volume of the molecule" more than the latter substitution. (Tr. 208:8–11; 208:22–209:1)

109. Indeed, the easiest way to make the methyl derivative of 2'-CDG (the bond that Dr. Schneller opines is a "conservative" addition) would be to make the double bond compound such as entecavir first, and then do "a very trivial reaction" to entecavir to arrive at Dr. Schneller's methyl substitution. (Tr. 208:15–21; 209:2–6; 1208:10–1209:24)

110. The substitution of a carbon-carbon double bond (the addition of the exocyclic methylene group) at the 5 prime position of the 5-membered ring of 2'-CDG results in entecavir. (Tr. 211:2–22; 219:19–220:7; DDX 60) Thus, the only difference in the molecular formulas of 2'-CDG and entecavir is a single carbon atom. (Tr. 211:16–22; 220:3–7; 1205:2–1206:6)

111. Accordingly, then, an ordinary medicinal chemist would have thought to make this substitution as of October 1990. Indeed, the prior art shows that others were, in fact, making similar substitutions at the time. As Dr. Schneller agreed, exocyclic methylene groups were "not a new concept in the 1980s" and a number of researchers were using them with "nucleoside analogs." (Tr. 1218:8–14, 1226:14–17) The evidence showed that, as Dr. Heathcock opined, in the 1989 timeframe, "an ordinary medicinal chemist would have thought of making this type of substitution to a nucleoside analog." (Tr. 211:23–212:4)

112. For example, there were numerous articles published in the late 1980s that disclosed a series of carbocyclic nucleoside analogs that had been synthesized with exocyclic methylene substitutions at the 2 prime position. (JTX 83.0001 ("Takenuki") (compound 4); JTX

88.0008-09 ("Ueda") (compound 16 & Scheme 4); Tr. 216:5–217:15; 1218:22–1222:15) At least two of these compounds with the exocyclic methylene group addition "exhibited potent activity" against HSV-1 and HSV-2 based on preliminary test results. (JTX 88.010; Tr. 217:17–23)

113. As to exocyclic methylene substitutions made at the 5 prime position, at least one other group of researchers had reported on having made such a substitution before Dr. Zahler did. Dr. Zahler was aware of this piece of prior art—the Madhavan reference—when he conceived of entecavir, and other medicinal chemists had to be as well. (Tr. 816:10–14)

114. In 1988, this group of medicinal chemists at Syntex (the "Madhavan group") selected the carbocyclic nucleoside analog known as aristeromycin as a lead compound. (Tr. 212:8–14; JTX 81; DDX 61) Aristeromycin is an analog of the nucleoside adenosine, and it itself had toxicity associated with it. (Tr. 212:12–16; 1240:13-24) Nevertheless, the Madhavan group worked with aristeromycin and made an analog of it by substituting an exocyclic methylene group at the 5 prime (or 6 prime) position ("Madhavan 30"). (JTX 081.0002–03 (compound 30); DDX 61; DDX 103 (Madhavan 30); Tr. 212:5–213:3) Their research was published in a 1988 *Journal of Medicinal Chemistry* article. (Tr. 213:4–10) Madhavan 30 was found to have antiviral activity against herpes and other viruses. (Tr. 214:1–7; 1234:6–13; JTX 081.0002–.0003) The Madhavan group also made analogs of aristeromycin that contained a fluoro substitution at the 5 prime position (compounds 10 and 24). (Tr. 213:1–2; 213:20–24; JTX 81.0001–.0003) Of the analogs made by the Madhavan group, they found that Madhavan 30 was the most potent, but also the most toxic. (Tr. 214:4–8; JTX 81.0002–.0003) However, the toxicity data would not "put off" a medicinal chemist from making similar substitutions, because

while it shows that the basic lead compound itself, aristeromycin, was "pretty cytotoxic," it was not clear whether that toxicity was triggered by the exocyclic methylene group itself or "due to the overall structure of [] the series they're working in." (Tr. 214:24–215:9)

115. Accordingly, the toxicity data reported by the Madhavan group would not have dissuaded the ordinary medicinal chemist working with 2'-CDG as a lead compound in October 1990 from substituting an exocyclic methylene group at the 5 prime position of the 5-membered ring of 2'-CDG. This is because the Madhavan group was working with an adenosine series of analogs as opposed to a guanine series. (Tr. 215:10–24) Aristeromycin was known to be cytotoxic while the toxicity of 2'-CDG was not yet well known at this time. (Tr. 216:2–4) Moreover, as Dr. Slusarchyk explained, toxicity data would not have deterred the ordinary medicinal chemist from "making more compounds in the area to investigate further." (Tr. 508:8–19)

116. In Dr. Schneller's expert report, when addressing the Madhavan group's results, Dr. Schneller stated that "[t]his mechanism of antiviral activity through toxicity to the host would certainly not suggest that one of ordinary skill in the art should make an antiviral molecule with a 6' exocyclic methylene group, *but it might not dissuade a person of ordinary skill in the art from making a molecule with a 6' exocyclic methylene group.*" (DTX 239.0029; Tr. 1228:13–1229:8) (emphasis added)

117. However, at his deposition, Dr. Schneller testified that the "Madhavan article *could have led* a person of skill in the art to seek drug discovery targets guided by combining the features reported in Madhavan with those in Shealy." (Tr. 1231:18–1232:2) (emphasis added) He also testified at his deposition that a person of ordinary skill in the art

would have had *no reason to believe* that adding a methylene at the 5 prime (or 6 prime) position would inhibit the binding of the molecule to the enzyme active site. (Tr. 1231:5-13)

118. Despite these prior statements, on direct examination at trial, Dr. Schneller stated repeatedly that a medicinal chemist of ordinary skill "*would not have been motivated* to combine" 2'-CDG and Madhavan 30 and in fact would have been "*discouraged*" from doing so. (Tr. 1123:21–1124:2; 1125:2–5; 1126:10–15; 1130:14–21; 1131:23–1132:3) (emphasis added) Dr. Schneller then went further, asserting that it would actually "*be out of the question*" for the ordinary chemist to think of combining 2'-CDG with Madhavan 30 during the relevant time period. (Tr. 1136:11–16) (emphasis added) In support of these statements, Dr. Schneller claimed that Madhavan and 2'-CDG have different "mechanism[s] of action" and therefore a chemist would have known that their combination would result in a "situation where probably no enzyme will be affected." (Tr. 1128:22–1131:5)

119. However, on cross-examination at trial, despite having earlier stated that Madhavan would have *discouraged* a medicinal chemist from making the exocyclic methylene substitution at issue to 2'-CDG, Dr. Schneller noted that it could be said that Madhavan "*would persuade*" a medicinal chemist to make that substitution. (DTX 239.0029; Tr. 1228:19–1229:18) (emphasis added)

120. In addition, although on direct examination Dr. Schneller had testified that that Madhavan and 2'-CDG have different "mechanisms of action" (and therefore a chemist would have known that their combination would result in a "situation where probably no enzyme will be affected"), on cross-examination, Dr. Schneller acknowledged that an ordinary medicinal chemist undertaking the traditional approach to drug discovery typically *does not know* anything

about "the mechanism of action of the [compounds] involved." (Tr. 1150:4–14) Instead, the idea is to learn about the compounds through the testing process. (*Id.*)

121. Moreover, Dr. Schneller acknowledged that his prior statements on direct examination—to the effect that researchers would have been discouraged from making this substitution—were "very different" from and in conflict with the statements that he had made to the contrary on cross-examination, in his expert report and in his deposition. (Tr. 1228:22-1232:17) He acknowledged that the statements he made in his deposition (including that Madhavan could have led a person of skill in the art to make the substitution at issue) and in his expert report were his honest opinions, were truthful, and that the Court could rely on them. (*Id.*)

122. Accordingly, an ordinary medicinal chemist would have had reason to combine Madhavan 30 and 2'-CDG by substituting an exocyclic methylene group at the 5 prime position of 2'-CDG "because there were other compounds like that that had already been made" and that chemist would expect the analog "to have similar biological properties to [2'-]CDG itself, which were good properties." (Tr. 219:5–18) As Dr. Heathcock testified, in light of the prior art, "the substitution of a methylene group to [2'-]CDG to arrive at entecavir" was an "obvious modification." (Tr. 221:8–14)

H. An Ordinary Medicinal Chemist's Expectation of Success In Making Entecavir

123. As discussed above, 2'-CDG and entecavir are structurally similar.

124. BMS designed an analog of 2'-CDG with an exocyclic methylene substitution at

the 2 prime position, and accurately predicted that it would have similar activity to 2'-CDG based on the modeling of their respective three-dimensional conformations. (Tr. 596:6-14; DTX 136.0004; DTX 141.0001-02, 0005-06)

125. Other evidence confirms that the addition of an exocyclic methylene group to a nucleoside analog such as 2'-CDG would not significantly alter its structure. The Ueda article disclosed that an antiviral nucleoside with an exocyclic methylene group "retains a similar overall conformation" to that of the parent natural nucleoside (i.e., the compound *lacking* the exocyclic methylene group). (JTX 88.0010; DDX 103 (Ueda #16); Tr. 217:24-218:19; 1224:1-5) That is, "[e]ven though the double bond had been added, it didn't change the three-dimensional shape of the molecule significantly." (Tr. 218:16-18)

1. An Ordinary Medicinal Chemist's Expectation Regarding Whether Entecavir Would Have Been Expected To Have Antiviral Activity

126. Based on the SAR approach using 2'-CDG as a lead compound, an ordinary medicinal chemist would have expected entecavir to also have antiviral activity. (Tr. 226:11-18) Dr. Heathcock explained that because entecavir and 2'-CDG "don't differ very much in structure" and since 2'-CDG "demonstrated good antiviral activity, a medicinal chemist of ordinary skill would have a very good reason to expect that entecavir . . . would have similar activity." (Tr. 226:18-24) Indeed, because of entecavir's similar structure to 2'-CDG, and because other nucleoside analogs containing an exocyclic methylene group had been made and shown to have antiviral activity, a medicinal chemist "would have a reasonable expectation that you could both make [entecavir], because there were other compounds like that that had already been made, and

that it would have similar biological properties to CDG itself, which were good properties." (Tr. 219:10-18)

127. The analogs with exocyclic methylene groups synthesized by the Madhavan group demonstrated that such substitutions resulted in compounds that retained the antiviral activity of the lead compound. (Tr. 227:1–6) For instance, as to the compounds aristeromycin and Madhavan 30 (where the only difference between the two is the presence of an exocyclic methylene substitution at the 5 prime position), those compounds showed similar activity. (Tr. 227:1-228:10; 1237:8-1238:23; DDX 63) Dr. Heathcock noted that the creation of Madhavan 30 was "a case where they made this kind of change[,] [i.e., exocyclic methylene substitution,] on a lead compound, and they got compounds with similar activity." (Tr. 228:8-10) Dr. Schneller had "no dispute" with Dr. Heathcock's analysis on this point. (Tr. 1239:11-21) Based on this precedent, an ordinary medicinal chemist would expect that if he substituted an exocyclic methylene group on 2'-CDG as a lead compound, that change would produce a compound with similar biological activity to 2'-CDG. (Tr. 228:11-17) This is the hypothesis known as SAR, which is the "the basic tenet by which medicinal chemists operate." (Tr. 145:2-14 ("[I]f you have two compounds that are similar in structure, they will have similar activity."))

128. As explained above, 2'-CDG showed potent antiviral activity. As also noted above, nucleoside analogs with exocyclic methylene substitutions were also found to possess antiviral activity. Therefore, when substituting an exocyclic methylene group on 2'-CDG to make entecavir, an ordinary medicinal chemist would have a reasonable expectation of success in ending up with a compound having similar antiviral activity to that exhibited by 2'-CDG. (Tr. 229:4-19)

2. An Ordinary Medicinal Chemist's Expectation of Success In Synthesizing Entecavir

129. Given that "synthetic organic chemistry" is the "stock and trade" of a medicinal chemist, and because the "tools that you need to make entecavir were all out there in the literature," an ordinary medicinal chemist would have been able to synthesize entecavir after having conceived of it. (Tr. 221:18-222:12)

130. Dr. Slusarchyk agreed. When Dr. Zahler went to him with the idea for entecavir, Dr. Slusarchyk immediately had a "very good idea" how to make it. (Tr. 503:10-14) Dr. Slusarchyk synthesized entecavir based in part on his "review of the literature," including the Biggadike reference. (Tr. 503:21-504:7; DTX 150.0002) Dr. Slusarchyk knew how to perform this synthesis because there were "tons of references" available. (Tr. 505:4-506:2) He explained that "like a good chemist should do" he simply needed to "just put the pieces together," (Tr. 506:17-18), and that this was something that was "generally known by chemists" and had been done for 70 or 80 years. (Tr. 506:3-11) Dr. Slusarchyk testified that he "expected to be able to [synthesize entecavir] with his skills as a chemist" when he learned of entecavir's conception. (Tr. 506:23-507:5)

I. Secondary Considerations of Non-Obviousness

1. Unexpected properties

a. Potency

131. The fact that entecavir would have antiviral activity against hepatitis B was expected. Before entecavir was even tested against the hepatitis B virus in 1994, (Tr. 598:20–599:6), the inventors represented that they "believed [entecavir] to be active against" a

variety of viruses, including "hepatitis B." (JTX 1.0003, col. 4:34–42; DTX 9.0008-.0009; Tr. 636:2–637:6) This belief was based on Dr. Zahler's "scientific judgment." (Tr. 637:9–11) As previously noted, at the time of entecavir's invention, BMS did not have an assay that could test a compound's activity against the hepatitis B virus, and so it was not then tested for that purpose. (Tr. 828:6–15)

132. A few years later, in 1994, when BMS developed a test for the hepatitis B virus against which to test compounds, Dr. Zahler was asked to select "a limited number" of BMS's compounds; entecavir was among those that he chose. (Tr. 638:18–641:10)

133. Entecavir was then tested for activity against hepatitis B, and it showed "extraordinary potency against" the virus. (Tr. 1036:2–8) Potency for hepatitis B treatment has two definitions: (1) the amount of drug needed to suppress the virus in a cell culture model (*in vitro*); and (2) the ability to reduce hepatitis B viral DNA to an undetectable level in a patient (*in vivo*). (Tr. 459:17–480:1; 1357:12–1358:19) Entecavir is more potent *in vitro* than every other tested compound, a fact that Teva's expert Dr. Thio acknowledged. (JTX 107.0003–.0004; Tr. 492:17–19 ("In vitro, entecavir is more potent than all of the other nucleotide and nucleosides")) However, what a treating physician really cares about is how potent or efficacious the drug is *in vivo*, not *in vitro*: "what we care about is how safe and effective the drug is . . . in a person." (Tr. 460:20–461:6)

134. When it comes to entecavir's *in vivo* potency, the drug is more potent than any of the hepatitis B drugs that were FDA-approved before it—entecavir works at a smaller dose. (Tr. 1358:22 –1360:20; *see also* Tr. 834:17–835:2) While more potent than previously-approved oral hepatitis B drugs, entecavir has a comparable potency to tenofovir, another hepatitis B drug.

BMS's expert, Dr. Gish, published a 2012 article noting that fact: "[i]n order of potency, the oral nucleos(t)ide analogues can be ranked in the following order: entecavir and tenofovir > telbivudine > lamivudine > adefovir." (DTX 238.0004) Likewise, in another 2012 article, Dr. Gish reported that "entecavir, telbivudine, and tenofovir are the most potent of the available NA antivirals" *in vivo*. (DTX 237.0002)

b. Resistance

135. Entecavir works by inhibiting hepatitis B viral replication at three independent steps in the replication process. In other words, in order for the virus to replicate in a patient who is taking the drug, "the polymerase has to change simultaneously in three points, three locations, to get around entecavir [so] [t]hree changes have to take place and then [the virus] can start replicating." (Tr. 1365:16–1366:16; JTX 126; DTX 107.0003)

136. Entecavir's high potency reduces resistance by providing less ability for the virus to mutate and develop resistance to the drug. (Tr. 1365:16–1366:5; DTX 237.0005–6; DTX 107.0003)

137. Entecavir has a very high genetic barrier to resistance. (Tr. 1415:10-1416:9; DTX 107.0003; DTX 238.0014; DTX 237.0005) A genetic barrier is defined as the number of primary mutations which are required for drug resistance to emerge, resulting in decreased drug efficacy and viral breakthrough. (DTX 237.0005; Tr. 1415:13-22) After six years of entecavir therapy, resistance to entecavir develops in only 1.2% of treatment naive patients (meaning patients who have not previously received treatment for hepatitis B). (Tr. 479:21-24; Tr. 1367:7-12; DTX 238.0007; DTX 237.0003; JTX 135.0019) Of the approximately 400 patients that Dr.

Gish has treated with entecavir, only one patient has developed "true entecavir resistance." (Tr. 1367:13-19)

138. Resistance to entecavir develops at a significantly lower rate than resistance to two other hepatitis B drugs that were FDA-approved before entecavir: lamivudine and adefovir. (DTX 237.0005; DTX 107.0003-.0004) For example, more than 70% of lamivudine patients develop breakthrough viral resistance by five years, and 29-42% of adefovir patients develop breakthrough viral resistance at five years. (Tr. 1339:14-20, 1341:15-1342:2; DTX 237.0003) However, resistance to tenofovir appears to be on par with resistance to entecavir in treatment naive patients—as to both drugs, such resistance is very rare. (Tr. 1414:11–12; 1415:7–9) In 2012 publications, Dr. Gish reported that tenofovir has no known resistance issues while entecavir's resistance rate ranges from 1 to 7 percent. (DTX 237.0003; DTX 238.0004) After analyzing various studies, Dr. Gish concluded that "the drugs that have shown the highest barrier to resistance in clinical studies in NA-naive patients are entecavir and tenofovir." (DTX 237.0003)

139. The resistance profile for entecavir is not as strong in lamivudine-resistant patients. In these patients, entecavir has a 30% rate of resistance after three years (JTX 135.0019), while adefovir has an 25.4% resistance rate in these patients after two years. (JTX 135.0018; Tr. 481:11–14) After five years, entecavir's resistance in these patients is almost as high as lamivudine's at 51% and 60–70%, respectively. (JTX 46.0020, .0016) On the other hand, entecavir is the drug of choice in adefovir-resistant patients. (Tr. 1369:15-1370:12)

c. Safety

140. Both parties' experts agree that entecavir is a very safe and effective drug.

(Tr. 446:1-3; *see also* 1356:16–22) Drs. Schneller and Zahler attested that entecavir has a large therapeutic window, meaning the range between the dose that effectively treats the hepatitis B virus versus the dose that displays toxicity. (Tr. 1097:17–1098:5; 833:7–24)

141. There is a warning on the Baraclude label about the potential that it could cause lactic acidosis; however, all nucleoside analogs have this "black box" warning in their prescribing information, as this side effect can occur with any of such drugs. (Tr. 1343:4-22, 1378:24-1379:8; JTX 47.0003; DTX 35) Dr. Gish testified that he has never seen any issues with lactic acidosis in his practice with patients using entecavir or tenofovir. (Tr. 1375:17-22)

142. Entecavir does not have any kidney or bone toxicity issues. (Tr. 1372:24-1373:10) Dr. Gish testified that tenofovir has been identified to have kidney and bone toxicity issues, although he noted that such effects were "rare" and "unusual." (Tr. 1373:11–18) Indeed, in 2009, Dr. Gish published an article reporting that "the risk of renal toxicity associated with tenofovir is 1% or less per year." (JTX 136.0004) Dr. Gish has personally treated two patients who he "believe[s] strongly" developed permanent kidney injury because they were taking tenofovir and were not having their dosages monitored by their local doctors. (Tr. 1376:6-24) And even in light of these possible (albeit rare) side effects, Dr. Gish testified that entecavir and tenofovir have "similar" safety profiles. (Tr. 1375:17–20)

2. Commercial Success

143. Baraclude, the commercial embodiment of claim 8 of the '244 Patent, provides an unquestionable benefit to hepatitis B patients who take the drug. (Tr. 493:10-13; 1284:6-12)

144. In the United States, BMS sold 50,000 units of Baraclude in 2006, its first full year of sales; by 2011, that figure had increased to 167,000 units. (Tr. 1275:11-18;

JTX 9.0001-.0006; JTX 10.0017; JTX 11.0001; JTX 29.0035; DTX 109.0001-.0002; DTX 240.0004-.0005) Baraclude has had increasing unit sales, period over period, since its launch. (Tr. 1275:4-18; 1266:6-17)

145. Worldwide, BMS earned $83 million from the sale of Baraclude in 2006, the drug's first full year on the market, and increased its revenues to $1.2 billion by 2011. (Tr. 1277:6–12; PTX 74 at 15-16; PTX 124 at 1-3; PTX 142 at 46) In the United States, Baraclude generated $50 million of revenue in 2006, $207 million in 2011, and $835 million total through 2011. (Tr. 1276:9-17, 1277:8-14; PTX 74 at 15-16; PTX 124 at 1-3; PTX 142 at 46) Overall, BMS's total revenues from worldwide sales of Baraclude from 2005 through 2011 is $3.8 billion. (Tr. 1277:12-16; PTX 137; PTX 138; PTX 139; PTX 140; PTX 142 at 46; PTX 143 at 33)

146. Teva is a "large generic global company" that develops many generic products. (Tr. 1265:18–23) When considering which brand-name products to copy, Teva looks to products that sold approximately $30 million per year, with a sales trend that was "flat or growing." (Tr. 1265:8-1266:5) Baraclude's sales clearly exceed this requirement. More broadly, however, Teva witness Mr. Marshall explained that when deciding whether to develop a generic drug, Teva takes "more of an exclusionary approach" whereby it looks for reasons not to make the drug. (Tr. 1265:12–23) Regardless, the fact that Teva is seeking approval to market a generic form of Baraclude is an indication that Baraclude is indeed commercially successful.

147. Baraclude's launch in 2005 caused a continuing decline in the U.S. market share of Hepsera (the brand name of adefovir), which had previously been the number one hepatitis B oral antiviral drug on the market. (Tr. 1281:19–1282:8, JTX 09.0001-.0006; JTX 10.0017; DTX 240.0002-.0005; PDX 161) Baraclude passed the other oral antiviral medications on the market

and established itself as the number one drug in the market by early 2009. (Tr. 1280:11-13; 1281:9-15; JTX 9.0001-.0006; JTX 10.0017; DTX 240.0002-.0005) By this time, Baraclude reached its peak market share of 36 percent. (Tr. 1280:20-1281:5; JTX 09.0001-.0006; JTX 10.0017; DTX 240.0003) While this figure eventually dropped to approximately 34 percent, in 2009 and 2010, after Viread (the brand name of tenofovir, Baraclude's primary competitor) entered the market, Baraclude thereafter "basically maintained its share of the market." (Tr. 1282:16-24; JTX 9.0001-.0006; JTX 10.0017; DTX 240.0003) At the time of trial, Baraclude and Viread had about equal shares of the market. (Tr. 1313:12–23; DDX 104; JTX 37)

148. While Baraclude has been commercially successful since its launch, its share of the market with regard to hepatitis B drugs has not been overwhelmingly robust, in that for all years that Baraclude has been available on the market, over half of the prescriptions written for hepatitis B treatments have been (and continue to be) written for another drug. (Tr. 1314:3–11; DTX 240.0002–.0003) When Baraclude entered the market in April 2005, its two main competitors were Epivir (the brand name for lamivudine) and Hepsera (adefovir). (Tr. 1293:10–20; DTX 240.0002; PDX 161) One year after Baraclude's launch in April 2006, Hepsera still had 55% percent of the market and Epivir had 29% of the market; Baraclude trailed behind with only 16% of the total prescriptions for hepatitis B. (Tr. 1299:14–1300:10; DTX 240.0002) By April 2008, three years after Baraclude's launch, Hepsera still had 42% of the market share while Baraclude had 33%. (Tr. 1300:15–20; DTX 240.0003) Baraclude finally caught up with Hepsera in terms of market share in October 2008. (Tr. 1300:21–1301:2; DTX 240.0003)

149. Indeed, BMS's former Senior Product Manager for Baraclude, Ms. Kawaljit Kaur,

confirmed that Baraclude was "somewhat slow to gain market share . . . [i]n comparison to what was expected [at BMS]." (Tr. 1252:22–1253:2; 1258:21–1259:3) Overall, BMS considered Baraclude's market share and sales performance to be "sub optimal," since it did not meet BMS's expectations. (Tr. 1261:16–1262:1)

150. Baraclude was also slow to gain market share in comparison to other hepatitis B drugs. (Tr. 1256:21–1257:13; 1263:1–4; 1303:9–15) For instance, by September 2003, one year after its launch, Hepsera had 41% of total prescriptions in the hepatitis B market (although, it should be noted, there was only one other competitor, Epivir, on the market at this time). (Tr. 1298:20–24; DTX 240.0002; PDX 161) Viread (tenofovir) entered the hepatitis B market in August 2008 alongside five competitors, including Baraclude, and was able to gain 26% of the market within a year, making it more successful at launch than Baraclude. (Tr. 1263:1–4; 1301:17–1302:20; DTX 240.0003)

151. A February 19, 2010 internal BMS "Brand Review" presentation notes that "Viread enter[ed] the CHB Marketplace & [took] the Lead Within 8 Months." (Tr. 1304:11–22; PTX 106.0038; *see also* JTX 008.0013 ("Viread grew to 28% market share in 10 months, a milestone which took Baraclude 30 months from launch to achieve")) A few months later, in May 2010, BMS sent an urgent memo to certain of its employees, instructing them to "Immediately Stop Using Materials with the #1 Prescribed Claim" as to Baraclude, because the market share data "now shows [that] Baraclude and Viread are roughly equal in market share"—a change that BMS had anticipated "for many months." (JTX 37; Tr. 1312:2–1313:1)

152. Baraclude's commercial success can primarily be attributed to its chemical

properties. For one thing, as compared to its primary competitors, Baraclude was priced at a premium. (Tr. 1285:10-1286:8; PTX 126; JTX 45) Accordingly, a low-pricing strategy did not drive the success of Baraclude. (Tr. 1287:23-1288:1)

153. The data also shows that sales of Baraclude do not appear to be directly tied to the money that it spends on marketing the drug. Since its launch in 2005, BMS has reduced the percentage of revenue that it has spent marketing, advertising, and promoting Baraclude. (Tr. 1289:8–13; PTX 74.0015–.0016) So for example, while BMS spent 46% of its Baraclude revenue in 2006 on marketing, advertising, and promoting Baraclude, in 2010 BMS spent 19% of its revenue on these activities. (Tr. 1289:8–13; PTX 124 at 1–3; PDX 168) Even so, Baraclude's sales have continued to increase over time, as indicated above. (Tr. 1275:4-18; Tr. 1266:6-17) While BMS's expert Mr. Tate did not quantitatively compare the dollars that other companies spent on the promotion of competitor drugs with the dollars that BMS has spent on the promotion of Baraclude, "qualitatively [he] was able to gain information from some of the documents [to suggest that such spending] was similar in nature." (Tr. 1295:15-1296:20) Therefore, he concluded that sales of Baraclude do not appear to be directly tied to the money BMS spends on marketing the drug. (Tr. 1289:14–22)

154. Finally, BMS's sales force is similar in size to that of the companies that produce Baraclude's previous and current primary competitors, Hepsera and Viread. (Tr. 1289:23-1290:9, JTX 13.0047) Thus, marketing efforts have not driven the sales of Baraclude (or at least have not done so to a greater degree than they have for any competitor). (Tr. 1290:10-13)

3. Failure of Others and Long-felt Need

155. The nucleoside analog field has been a fruitful area for hepatitis B research.

Between 1998 and 2008, there have been five oral medications that are nucleosides or nucleotides that have been FDA-approved for treatment of hepatitis B: lamivudine, adefovir, entecavir, telbivudine and tenofovir. (Tr. 420:11–19; 1413:4–7; DDX 105) Dr. Gish referred to the nucleoside analog field as "dynamic" in terms of hepatitis B drugs and characterized the decade as a time of "huge change." (Tr. 1413:4–14; 1431:5–11) Dr. Thio opined that the development of hepatitis B drugs is not marked by a history of failures "[b]ecause there are many drugs that were developed and actually came to market . . . [o]ver a period of eight years." (Tr. 458:15–459:2)

156. Other leading experts in the hepatitis B community agree, viewing the drug development history for hepatitis B as a success, not a failure. For instance, a May 2007 article concluded that "[s]ignificant advances in the management of chronic hepatitis B (CHB) have been made over the past decade. . . . due to the introduction of effective antiviral therapy." (DTX 49.0001) Likewise, a May 2011 article reported that "[s]ubstantial progress has been made in the treatment of hepatitis B in the past decade. The availability of medications that have potent antiviral activity and are safe for use in patients with cirrhosis has broadened the indications for hepatitis B treatment." (DTX 76.0001)

157. A 2003 chart published by the Hepatitis B Foundation listed a number of compounds then in development to treat hepatitis B. (JTX 48.0007; Tr. 1349:16–18) Of those compounds, sixteen are nucleoside analogs. (JTX 48.0007; Tr. 1346:10–14) Ultimately, four such compounds were ultimately approved by the FDA to treat hepatitis B (lamivudine, adefovir, entecavir and telbivudine). (Tr. 1350:2–7) Tenofovir, which was also later FDA-approved to treat hepatitis B, is not on the chart. (Tr. 1430:7-19)

158. The remaining nucleoside analog compounds on this list did not make it to market. (JTX 48.0007; PDX 1-02) Dr. Gish testified as to the specific reasons why three of those twelve remaining compounds were not FDA-approved for the treatment of hepatitis B. (Tr. 1347:14–1349:18) One such compound, FTC, was not approved to treat hepatitis B but is now sold in a combination pill with tenofovir to treat HIV. (Tr. 1347:14–18; *see also* 457:16–21) Another compound, DAPD, was stopped in Phase II trials because it not effective enough to warrant further development. (Tr. 1348:3–11) A third compound, L-FMAU, was abandoned during trials because it was found to be very toxic, although it is now approved for use in Korea and the Philippines. (Tr. 1348:20–1349:2; *see also* 458:1–4) As for the rest of those compounds, Dr. Gish testified that "most of the rest . . . just did not have a benefit that outweighed risk and would not justify further drug development." (Tr. 1349:5–8) On cross-examination, however, Dr. Gish clarified that he had "no idea" what happened to certain of the remaining nine compounds—including Robustaflavone and MCC478—because "[n]othing has been published on them." (Tr. 1429:3–1430:6)

159. According to Dr. Gish, the list of potential drugs set out in the Hepatitis B Foundation 2003 chart is not an exhaustive list of therapies that were in development for treatment of hepatitis B, but ultimately did not make it to market. (Tr. 1349:19-1350:1)

160. While Dr. Gish testified that certain drugs on this chart were examples of drugs that have failed in this field, Dr. Thio pointed out that Dr. Gish labeled these drugs as failures not because they failed to produce antiviral activity, but because they had failed to be approved for use by the FDA. (Tr. 454:19–456:10) Dr. Thio noted that there are many reasons why a drug might not progress to a stage where it obtains FDA approval, and that some of those reasons,

such as financial considerations, do not have anything to do with the drug's laboratory results. (Tr. 458:5–14)

161. Hepatitis B is a worldwide disease. (Tr. 471:1–4; 1332:8–10; *see also* DTX 104 "[Hepatitis B] is a major global health problem.")) Across the globe, there are an estimated two billion people infected with the virus and 350 million people infected with chronic hepatitis B. (Tr. 471:5–8; DTX 104) Worldwide, 600,000 to one million people die each year from the disease, "a very large number." (Tr. 1327:9–12; DTX 104) The World Health Organization places hepatitis B virus in the top ten causes of death worldwide. (Tr. 1332:11–17; JTX 135.0001) In the United States, there are an estimated 1.25 million people infected with the virus, which amounts to less than one percent of the country's population. (Tr. 404:4–9; 471:5–9; PTX 456.0001) Likewise, in western Europe, less than one percent of the population is chronically infected. (DTX 104.0002)

162. In 1990, the hepatitis B statistics were similar to current statistics. At that time, worldwide estimates "suggest[ed] that chronic hepatitis B virus (HBV) infection [was] the most important chronic viral infection affecting humans," while the virus was "uncommon" in the United States and other developed areas of the world and "not usually listed as a major cause of illness or death." (PTX 456.0001)

163. The hepatitis B virus infects the liver and is spread by person-to-person contact with bodily fluids. (Tr. 396:7–15; 1325:4–12) Hepatitis B frequently causes mild symptoms, but in some cases it can cause severe symptoms such as liver cirrhosis with a risk of liver failure and well as liver cancer. (Tr. 400:1–19; 1327:3–9) Approximately fifteen to forty percent of the

people infected with chronic hepatitis B are at risk of ending up with end stage liver disease and liver cancer. (Tr. 410:5–9; 1327:3–9)

164. In the early 1980s, a vaccine was introduced that is over 95% effective at preventing hepatitis B. (Tr. 405:7–20; DTX 104.0001) Accordingly, because of the vaccine, fewer people ultimately need treatment for the virus "[b]ecause there are fewer people who get infected with hepatitis B." (408:6–13) It is undisputed, however, that the vaccination has no role and thus no benefit to the 350 million people chronically infected with hepatitis B. (Tr. 471:23–472:6; 1333:20–23)

165. It is also undisputed that there is no cure for hepatitis B. (Tr. 399:3–10; 423:10–17; 1330:10–13) As long as the disease has been around, there has been a need for a cure; that remains the case today. (Tr. 423:10–17; 1389:13–17) As Dr. Gish put it, the fact that there is no cure for hepatitis B is "[a] major issue." (Tr. 1389:20–23)

166. Until a cure is found, the aims of treatment "are to achieve sustained suppression of HBV replication and remission of liver disease" and to "prevent cirrhosis," liver failure, and liver cancer. (JTX 46.0010; *see also* DTX 107; Tr. 415:3–13; 1333:24–1334:20)

167. Not all people that contract hepatitis B require drug therapy, because not all have the disease "severe enough that they will get [] end stage problems." (Tr. 403:9–14) About 95% of adults with normal immune systems who contract the acquire the disease "clear the virus from the blood" without treatment. (Tr. 1326:9–16) As of 2008, there are seven FDA-approved drugs available for the patients that require drug therapy, one of which is entecavir. (Tr. 409:9–24; DTX 237.0002) All of these drugs save lives. (Tr. 424:7–10)

168. At the time of entecavir's approval in 2005, there were three FDA-approved drugs

for the treatment of chronic hepatitis B: standard interferon (also referred to as injectable interferon alfa), lamivudine, and adefovir. (JTX 120.0008; DTX 107.0001-.0003; Tr. 1336:1–12, 1338:3–7, 1341:2–8; PDX 107)

169. The first FDA-approved drug for treating hepatitis B was standard interferon, which was approved in 1991. (Tr. 418:5–8; 1336:8–12; DTX 107.0001) This drug seemed to be a "major breakthrough" at the time, because for the first time, people with hepatitis B could be treated. (Tr. 418:7–11) Dr. Gish acknowledged that this treatment was "an improvement" over the status quo prior to its introduction, which was that there was no treatment for the hepatitis B infection. (Tr. 1390:6–12) However, standard interferon was not an ideal treatment, in that it is administered as an injection that the patient must give herself, it causes "lots of side effects," and it is only effective in a small subset of patients. (Tr. 418:11–22; 477:11–478:4; 1336:11-22; JTX 135.0016) Due to these significant shortcomings, interferon alfa did not meet the need for an effective long-term treatment for HBV-infected patients. (Tr. 418:5-22; 419:7-16; 1337:10-16)

170. Pegylated interferon was FDA-approved in 2005. (Tr. 447:3–5) One of the three "first line" or preferred therapies for treating hepatitis B today, pegylated interferon is easier to administer and lasts longer than standard interferon. (Tr. 447:4–448:2; 1334:21–1335:3; 1390:23–1391:3) According to Dr. Gish, while pegylated interferon is listed as a first line therapy, it is rarely used today. (Tr. 1390:23–1391:3)

171. In addition to the two approved interferon therapy treatments, there today are five FDA-approved oral medications that can treat hepatitis B, all of which are nucleosides or nucleotides: lamivudine, adefovir, entecavir, tenofovir and telbivudine. (Tr. 420:11–19; DDX

105) All of these drugs were approved by the FDA between 1998 and 2008. (Tr. 420:11–19; 1413:4–7; DDX 105) Dr. Thio characterized this time period as "an explosion of . . . hepatitis B treatments in a relatively short period of time." (Tr. 420:18–421:1) A 2011 review article on hepatitis B therapies noted that "[s]ubstantial progress has been made in the treatment of hepatitis B in the past decade. Many safe and effective drugs are now available." (DTX 76.0008; Tr. 421:7–422:19) BMS's expert Dr. Gish acknowledged that the time period between 1998 and 2008 was a period of "substantial advancement in the treatment of hepatitis B," deeming it "a huge change." (Tr. 1413:4–14)

172. Lamivudine, invented by 1989, was the first FDA-approved oral drug used to treat chronic hepatitis B, as it was approved in 1998. (DTX 107.0002; JTX 85; Tr. 424:11-19; 1338:6-9) Dr. Thio noted that lamivudine's approval "had a huge impact," as the oral medication "ushered in a new era for therapy of hepatitis B" because it "was a very safe drug" that doctors could "give to whoever [they] wanted"—as opposed to the small subset of patients that could be treated with interferon. (Tr. 424:17–425:6) Dr. Gish agreed that the period following lamivudine's introduction it was a "[b]riefly" optimistic time. (Tr. 1395:7–14) Indeed, Dr. Gish prescribed lamivudine in his practice and he was personally involved with clinical studies on the drug that he published in the *New England Journal of Medicine*, a widely respected journal in the field. (Tr. 1394:16–1395:18; 1427:3–7)

173. In 1999, an article was published that reported on some resistance caused by lamivudine, although the problem was not fully appreciated for a few more years. (Tr. 430:9–431:2) However, by 2001, doctors appreciated that lamivudine caused drug

resistance in many patients the longer they took it, meaning lamivudine could no longer meet the treatment needs of those patients. (Tr. 429:3-431:2; 431:9–15; 1395:16–1396:20) While lamivudine is no longer a first line therapy for chronic hepatitis B infection, (Tr. 1371:1–6), it is still an effective drug in patients that do not experience resistance. (Tr. 431:21–432:4)

174. Shortly after physicians realized the resistance problems with lamivudine, in 2002, adefovir was approved by the FDA for the treatment of hepatitis B. (Tr. 432:23–433:1; 1396:15–23 ("Adefovir came just to follow.")) Dr. Gish and Dr. Thio agree that adefovir, invented in 1986, was also met with optimism when it was approved. (JTX 77; Tr. 433:12–23; 435:14–21; 1408:16–17) Adefovir's initial rates of resistance were very low, especially when compared to lamivudine. (Tr. 433:12-23, 435:4-21; 1408:18-23) A 2004 review article on hepatitis B treatments advised that "[p]atients requiring therapy for longer than 1 year probably are treated best with adefovir, with its much lower incidence of resistance. Adefovir has similar efficacy to lamivudine and is well tolerated." (JTX 120.0016; Tr. 434:14–436:1) According to Dr. Gish, adefovir met the needs of hepatitis B-infected patients for "one to two years" after its approval in 2002, but doctors then began to realize that patients were developing resistance to adefovir. (Tr. 1341:15-1342:2) By 2007, five years after its approval, approximately 27 to 42 percent of patients had developed resistance to adefovir. (Tr. 1341:15-1342:2; DTX 237.0003) In addition to the resistance problems, by two and three years after its approval, physicians realized that adefovir was causing kidney problems in patients. (Tr. 1342:12–22; 1410:6–7)

175. Dr. Gish prescribed adefovir until 2005 and, up until that point, he had educated healthcare professionals about adefovir's useful properties while consulting for adefovir's manufacturer. (Tr. 1380:3–4; 1409:10–18) But by 2005, the hepatitis B community had

"realized Adefovir was a major problem." (Tr. 1409:1–2) Adefovir is no longer a first line therapy. (Tr. 1371:1–6) It is still used, however, and is the preferable treatment for patients with lamivudine resistance if tenofovir is unavailable. (DTX 107.0003)

176. Tenofovir, a nucleotide analog, was invented in 1986 and was approved by the FDA in 2001 for treating HIV (not the hepatitis B virus). (Tr. 436:17-22; JTX 77.0020 (compound 2)) By 2002, however, doctors were prescribing tenofovir "off label" to treat hepatitis B, but such use was confined to a very small fraction of hepatitis-infected patients—those who were also infected with HIV ("co-infected" patients).[9] (Tr. 417:7–18; 1377:14–24) During the early 2000s, approximately 10% of people outside of the United States infected with hepatitis B were co-infected with HIV; that percentage was even smaller in the United States, where approximately 1% of those hepatitis B patients were co-infected. (Tr. 1433:6–1434:13) By 2005, tenofovir's off-label use for hepatitis B was still experimental, and limited to only about 1% to 3% of hepatitis B patients. (Tr. 1377:18-1378:2) It is undisputed that the off-label use of tenofovir between 2001 and 2005 was largely limited to co-infected patients, because doctors who treated HIV-infected patients were well aware of tenofovir. (Tr. 436:23-437:11, 439:9-12; 441:8-442:1, 482:10-23, 484:9-15, 485:19-486:9; 1377:14-1378:5, 1397:4-22, 1432:23-1433:5)

177. However, it is also not significantly disputed that among these physicians, tenofovir was quickly seen as a promising drug for the treatment of hepatitis B. Both Dr. Thio and Dr. Gish (who treated mostly non-infected hepatitis B patients, meaning they were not co-

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[9] Prescribing a medication "off-label" means prescribing the drug for a non-FDA-approved use. (Tr. 417:12–18)

infected with HIV) were prescribing tenofovir by 2002 to treat hepatitis B patients with "great responses" and no safety or resistance problems. (Tr. 437:6–16; *see also* 1398:19–1399:3) These results even prompted Dr. Gish to encourage Gilead, tenofovir's manufacturer, to obtain a hepatitis B FDA indication for tenofovir. (Tr. 1412:13–18) Dr. Gish then worked with Gilead on the development of tenofovir. (Tr. 1322:23–1323:1) Dr. Gish testified that "the data on Tenofovir's benefit for patients I think became pretty visible around 2004." (Tr. 1378:11–13)

178. Literature was also being published on the use of tenofovir to treat hepatitis B well before its approval for that indication in 2008. Although the Hepatitis B Foundation's Spring 2003 newsletter's chart of hepatitis B drugs in development did not include tenofovir (JTX 48.0007), another section of the newsletter entitled "Hepatitis B Clinical Trials" reported a new "Phase II Comparison of Adefovir and Tenofovir for the Treatment of Lamivudine-Resistant HBV" study. (JTX 48.0017) In that study, researchers were "compar[ing] the combination of adefovir and lamivudine with the combination of tenofovir and lamivudine to determine which drug combination is most effective in people who are infected with both HBV and HIV." (*Id.*) A review article on hepatitis B treatments published in February 2004 discussed "[s]everal studies confirm[ing] that tenofovir is effective against both HIV and HBV." (JTX 120.0015; Tr. 440:24-442:1) The article did, however, note "reports of renal toxicity and hypophosphatemia associated with tenofovir therapy." (JTX 120.0015; Tr. 487:13–488:9) However, as previously noted, Dr. Gish testified that side effects of tenofovir involving "kidney issues" and "bone issues" ultimately have been "rare or unusual." (Tr. 1373:11–18; *see also* JTX 136.0004 (stating that "the risk of renal toxicity associated with tenofovir is 1% or less per year")) A 2007 article published in *Hepatology*, the lead liver journal, noted that "[t]enofovir has also been reported in

clinical studies to be effective in suppressing lamivudine-resistance HBV," citing to studies that had been published in 2004. (DTX 75.0009; Tr. 438:1–440:19) Dr. Thio opined that one of those 2004 studies would have helped readers understand that "people who are hepatitis B monoinfected could also respond well to Tenofovir." (Tr. 438:2–44:19; DTX 75.0009) Another 2007 review article on the management of chronic hepatitis B reported that "[tenofovir] has been used off label for those with severe [lamivudine] resistance before the approval of [adefovir] in 2002." (DTX 49.0006; Tr. 1403:18–1405:19)

179. Tenofovir was approved by the FDA for treatment of chronic hepatitis B in 2008. (Tr. 436:19-22; 443:3–8; 1350:14–15; 1377:6-13; DTX 107.0004) Since gaining FDA approval, tenofovir has joined entecavir as one of the first-line therapies for hepatitis B. (JTX 46.0001; Tr. 444:21-445:1, 446:1-7)

180. As noted above, entecavir was approved by the FDA on March 29, 2005, for the treatment of chronic hepatitis B. (Uncontested Facts at ¶ 22) Entecavir is clearly an effective, important drug that has saved lives and continues to do so today. (*See* Tr. 424:7–10)

181. Dr. Gish testified that the approval of entecavir in 2005 marked a "profound shift" in the treatment of chronic hepatitis B patients. (Tr. 1379:22-1381:18) Indeed, an article that Dr. Thio cited in her expert report, (Tr. 491:9–18), pointed to 2005 as ushering in "revolutionary improvement of patient outcome": "[s]ince 2005, better control of this disease through more profound suppression of viral replication is now achievable . . . ." (DTX 107.0004; Tr. 493:20-494:7) The article noted that "[i]n 2005, entecavir came [into] the arena . . . ." (DTX 107.003) Entecavir became a first line therapy for hepatitis B treatment at that time, while lamivudine and

adefovir were moved to second- and third-line therapies. (Tr. 446:1–7; 1371:1-1372:3; JTX 46.0001; JTX 136.0003-.0004)

182. Dr. Thio described entecavir as an "effective" drug and "very safe [] to take." (Tr. 446:1–3) Dr. Gish agreed, characterizing the drug as "very impressive" because compared to previous treatment options, it showed better viral control, extremely rare resistance, and extremely rare side effects. (Tr. 1356:16–22; DTX 238.0004) In treatment-naive patients, entecavir controls the hepatitis B virus in 90 to 95% of patients. (Tr. 1355:24-1356:8; DTX 107.0003-.0004) And upon entecavir's introduction, complications that had accompanied cirrhosis, such as liver failure and jaundice, started to disappear from clinical practice (although these results were also seen in a smaller subset of patients treated with lamivudine and adefovir). (Tr. 1355:24-1356:22, 1379:22-1381:18; *see also* JTX 136.0002 (attributing the decrease in cases of liver failure and less need for liver transplants to "the increased use of antiviral drugs" generally))

183. While entecavir is an effective, important drug, so too is tenofovir. It is undisputed that in treatment-naive patients, entecavir and tenofovir are "comparable" in terms of having high barriers of resistance, suppressing the hepatitis B virus and normalizing liver levels. (Tr. 446:8–23; 1375:6–16; 1410:19–1411:8; 1416:6–9; 1418:13–15; JTX 046.0012 (Table 8)) Entecavir is also similar to the other hepatitis B oral medications in that it must be taken long-term to avoid a high risk of virus replication. (Tr. 423:19–424:1; JTX 46.0020 ("only 7 (3%) had sustained suppression of HBV DNA to undetectable level 24 weeks off-treatment"))

184. And also like the other hepatitis B drugs, entecavir has resistance problems in

certain patient populations. In patients with lamivudine resistance (a large group, since lamivudine has been FDA-approved since 1998), tenofovir is the drug of choice over entecavir, as many of those patients will develop resistance to entecavir, such that entecavir does not meet the need to treat those patients. (Tr. 448:3–21; 449:4–16; 461:16–462:3; 477:7–9; 1370:13–23; 1375:10–14; DTX 107.0003; JTX 46.0026-.0027, .0020 ("Preliminary data indicate that entecavir resistance increased to 51% of patients after 5 years of entecavir treatment in lamivudine-refractory patients."))

185. However, entecavir is the drug of choice over entecavir for patients with adefovir resistance. This is because of the increased risk that such patients will develop resistance to tenofovir, and because entecavir has the most powerful level of viral suppression in those patients. (Tr. 1369:15–1370:12; 1374:21–1375:3; JTX 136.0003–.0004; JTX 46.0026)

186. Entecavir's approval in 2005 did not suppress the need for additional hepatitis B treatments. (Tr. 423:15–424:6; 449:17–24) Telbivudine, another nucleoside analog that is more potent than lamivudine with less resistance, was approved in 2006. (Tr. 449:21–22; 1412:19–23) And, as stated above, tenofovir received FDA approval for hepatitis B in 2008. (Tr. 436:19-22; 443:3–8; 1350:14–15; 1377:6-13; DTX 107.0004)

187. Dr. Gish stated that there was a need for a new treatment of hepatitis B between 2002 and 2005, yet Dr. Gish himself prescribed adefovir until 2005 and he touted the drug's good properties up until that time. (Tr. 1380:3–4; 1409:10–18)

4. Skepticism of Others

188. BMS's expert Dr. Gish testified that he and "most of the people in [his]

community" were skeptical that a single drug such as entecavir could control hepatitis B in their patients. (Tr. 1352:10–1353:9; *see also* Tr. 1353:6–9 ("[W]e were just thinking that one single drug was not going to ever be able to make it, to help our hepatitis B patient to be taken alone."); Tr. 1353:15–20 ("[T]he general view was . . . that a single drug would not be able to overpower this and suppress this and prevent resistance, prevent breakthrough.")) Dr. Gish did *not* testify that he and others were skeptical that entecavir would not be effective in treating hepatitis B; rather, the skepticism was apparently that entecavir would not work as a single form of treatment.

189. In 2001 and 2002, as entecavir was going through development and clinical trials, "there was a lot of homework that was being done at that time about" the benefit-risk ratio of entecavir. (Tr. 1352:2–9) Dr. Gish testified that he discussed the skepticism that he felt with other treating physicians at "[m]any different meetings and [in] consultation[s] and [with] advisory boards." (Tr. 1353:10–13) Dr. Gish also stated that he expressed his skepticism about entecavir to BMS, even calling a meeting for the purpose of reviewing all of the literature available on entecavir. (Tr. 1354:10–1355:11) During this meeting among physicians, BMS employees in the drug development program, independent consultants, and toxicologists, the *in vitro* data on entecavir was reviewed and the compound was given "the green light to proceed through the Phase 2/3 trial development for licensing." (Tr. 1354:19–1355:20; 1426:6–9)

190. Dr. Gish never published anything documenting this initial skepticism. (Tr. 1425:13–23) At trial, BMS did not produce any literature expressing initial skepticism about entecavir.

191. In fact, in the spring of 2003—two years before entecavir received FDA

approval—the Hepatitis B Foundation published the chart entitled "HBF Drug Watch: HBV Compounds in Development," listing, among other drugs either approved or in development, entecavir. (JTX 48.0007; Tr. 1344:12–1345:14) At the time, entecavir was going through Phase III testing. (JTX 48.0007) Dr. Gish explained that the purpose of the chart was to "keep[] up the hopes for patients in the hepatitis B world that there were drugs either approved or in development that would allow us to reach the next phase of successful management of our patients." (Tr. 1345:16–23)

192. Teva's expert Dr. Thio disagreed with Dr. Gish's opinion that entecavir was initially surrounded by skepticism. (Tr. 466:5–12) As Dr. Thio explained, given the promising *in vitro* data that entecavir displayed against the hepatitis B virus, "there was no reason to be skeptical that it wouldn't work well in humans," and, "if anything, people should have been optimistic about [entecavir based on these lab results and say] [i]t's probably going to work well on humans. I can't wait to try it out." (Tr. 466:12–18; 467:2-7) Dr. Thio did testify that as a treating physician she did not "take any of entecavir's in vitro characteristics into account in deciding" whether to give entecavir to a patient, because what she cared about was "how safe and effective the drug is . . . in a person"; however, this perspective is necessarily a different one than that of a physician consulting with a pharmaceutical company about drug development. (460:20-461:6; 466:12-18) Indeed, *in vitro* data is what Dr. Gish and others had reviewed at Dr. Gish's meeting with BMS, which resulted in entecavir getting the "green light" for further development. (Tr. 1354:19–1355:20; 1426:6–9)

5. Copying

193. Teva admits that it has copied the claimed invention, which covers entecavir.

(Uncontested Facts at ¶ 42) There are currently seven FDA-approved drugs available to treat hepatitis B, but Teva has chosen to copy entecavir. (Tr. 409:9–24; DTX 237.0002; Uncontested Facts at ¶ 24)

III. FINDINGS OF FACT RELATED TO INEQUITABLE CONDUCT[10]

A. Background Regarding Allegations

194. Teva has asserted that the '244 Patent is unenforceable due to inequitable conduct before the PTO. (D.I. 54 at ¶¶ 7-52) Teva initially accused both inventors of the '244 Patent (Dr. Zahler and Dr. Slusarchyk) and the two patent attorneys who prosecuted the patent application (Mr. Venetianer and Mr. Davis) of inequitable conduct, asserting that these individuals knowingly withheld and failed to disclose four references that discuss 2'-CDG from the PTO, with the intent to deceive the PTO. (*Id.*) The four references at issue were Shealy 1984, the Shealy '255 Patent, Marquez and Shealy 1987. (*Id.* at ¶ 8) Teva's inequitable conduct charge is premised on the fact that 2'-CDG was not cited to the Patent Office. (Tr. 54:6-10)

195. On June 25, 2012, Teva withdrew its allegation of inequitable conduct against Dr. Slusarchyk. (D.I. 124 at 3, n.1) Therefore, at trial, Teva pursued inequitable conduct allegations against Dr. Zahler, Mr. Venetianer and Mr. Davis.

B. 2'-CDG and the Invention of Entecavir

196. When Dr. Zahler came up with the idea for entecavir, he was not thinking about

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[10] The facts cited in Section III of the "Findings of Fact" portion of this Memorandum Opinion are those not previously cited in the "Findings of Fact" portion and that bear on the issue of inequitable conduct. Facts cited in prior "Findings of Fact" sections may also be relevant to this issue.

2'-CDG. (Tr. 542:6-12; 546:3-9) Instead, he was inspired by the natural 2'-deoxyguanosine and by lobucavir. (Tr. 542:18-543:23; 803:9-804:8; *see also* Tr. 651:20-652:2; 959:21-960:3; 962:2-9; 962:20-963:1; 967:13-18) Therefore, 2'-CDG did not play a role in Dr. Zahler's initial conception of the idea for the structure of entecavir. (Tr. 854:8-859:22; 864:5-865:1; 881:6-9)

197. As previously noted, Dr. Zahler first came up with the idea for entecavir in his head and drew it out on paper. (Tr. 552:6-16; Tr. 811:12-23) Then, because he tended to think in "three dimensions," Dr. Zahler used the Dreiding models in order to further develop his idea. (Tr. 552:12-16; 796:2-22; 811:17-812:11; PDX 531)

198. After Dr. Zahler used the Dreiding models to conceive of entecavir, his team proceeded on to use the proprietary computer-based computational model in order to better predict entecavir's preferred conformations, to see if entecavir's conformation was similar to those compounds that had antiviral properties, including lobucavir. (Tr. 553:1-554:16; 559:1-10; 562:9-18; 651:22-652:19; 812:12-813:24) At this point, in Dr. Zahler's mind, the factor that distinguished entecavir from 2'-deoxyguanosine was the addition of the exocyclic methylene group. (Tr. 812:21-22; 815:13-16) However, he had great concern about what the impact would be of adding the exocyclic methylene group to the natural nucleoside. (Tr. 814:1-815:16) Dr. Zahler therefore had Dr. Tino and Dr. Goodfellow perform the computer modeling regarding the structure of entecavir, which ultimately demonstrated that entecavir did indeed "overlap nicely" with 2'-deoxyguanosine. (Tr. 553:14-17; 816:23-817:10; 969:14-19)

199. In performing this computer modeling in May 1990, Dr. Zahler's team selected several different compounds to compare to entecavir via computer modeling and to help validate the computer model. (Tr. 559:11- 561:11; 563:3-564:3; 969:20-970:14) As previously noted,

these compounds included lobucavir, the natural nucleoside 2'-deoxyguanosine, and 2'-CDG (but did not include Madhavan compound 30). (Tr. 559:11- 561:11; 654:7-655:7; 670:8-671:6; 975:15-18) The only two compounds used in this computer modeling and validation process that were not compounds originally synthesized at BMS were the natural nucleoside and 2'-CDG. (Tr. 560:14-561:11; 658:10-15) 2'-CDG was chosen for use in this process as a "positive control," in that it had shown antiviral activity. (Tr. 564:4-13; 569:22-570:4) As BMS continued this modeling process, they refined the model; eventually the results showed that both entecavir and 2'-CDG demonstrated similar conformations to lobucavir, suggesting they might have similar antiviral properties to lobucavir. (Tr. 658:19-660:18) Dr. Zahler was aware of these testing procedures and results, as he was "heavily involved" in this process. (Tr. 660:21-24)

200. Once the computer modeling showed that entecavir could have promising antiviral properties, Dr. Zahler's team then set out to synthesize entecavir. (Tr. 817:2-818:8) As noted above, after six months, Dr. Slusarchyk and his associate at BMS were able to do so. (Tr. 822:11-823:15) Shortly thereafter, entecavir was tested for antiviral activity. (Tr. 827:12-14) Those test results showed that entecavir had modest but real activity against HSV-1, HSV-2 and VZV. (Tr. 828:1-5) Entecavir's activity against HSV-1 was fourfold less than that of acyclovir, the standard in the field. (Tr. 828:1-5; 829:2-4) It was not tested against hepatitis B at that time, because BMS did not have a hepatitis B assay. (Tr. 828:6-15)

201. Due to the modest initial test results for herpes activity and against VZV, as was previously noted, entecavir was not further developed and was instead "put on the shelf" at BMS. (Tr. 828:16-829:1) Only years later, in late 1994, was entecavir tested against hepatitis B. (Tr.

829:10-830:1) This came about because by late 1994, BMS had developed a hepatitis B assay, and Dr. Zahler selected entecavir as one of 20 compounds to test in that assay. (Tr. 830:2-16)

202. Even this testing of entecavir took some time, because when BMS employees looked to find the sample of entecavir in its storage facility, they discovered that the entecavir sample was lost. (Tr. 831:17-832:7) Only after searching for the sample for some time was it found, and testing began. (Tr. 832:10-833:1) The results of this testing were that entecavir was found to be very potent and effective against hepatitis B. (Tr. 833:7-838:4)

C. Individuals Accused of Inequitable Conduct and Their Respective Roles Regarding the '244 Patent Application and Other Applications

1. Dr. Zahler

203. As an inventor on more than one patent, Dr. Zahler was aware of his duty of candor to disclose material prior art to the PTO at the time of the '244 Patent application. (Tr. 516:4-517:5) The way he generally fulfilled that obligation was to communicate with attorneys at BMS about material prior art that he was aware of, as that art related to a particular application. (Tr. 517:6-9; Tr. 523:7-14; 844:9-15) These attorneys came to Dr. Zahler for this information because Dr. Zahler was the expert in the field, while the attorneys were not. (Tr. at 517:11-15)

204. One of the types of prior art that Dr. Zahler knew would be material to the PTO regarding a patent application would be scientific literature that disclosed structurally similar compounds to the compound that was the focus of the application. (Tr. 525:1-13; 526:13-527:8) In looking for relevant prior art, Dr. Zahler would typically focus on what he felt was the primary feature of the structure of the compound-at-issue—the feature that was "most

distinguishing"—and he would seek to provide prior art that contained that feature. (Tr. 845:2-6) Dr. Zahler would identify this prior art either from memory, from looking in his files or by doing a computer search. (Tr. 845:13-21)

205. After a patent application was filed, Dr. Zahler would have very little contact with the prosecuting attorneys at BMS regarding the application, since the attorneys handled correspondence with the Examiner. (Tr. 843:1-15) Now and then, if the attorneys had received comments from the Examiner, they would ask Dr. Zahler to look at those comments and to help them come up with appropriate scientific arguments in response. (Tr. 843:1-20)

206. At the time Dr. Zahler started working on entecavir, he was aware of 2'-CDG, and knew that scientists at SRI had worked with 2'-CDG. (Tr. 531:1-22) In his testimony at trial, Dr. Zahler stated that he knew, at the time of entecavir's invention, that 2'-CDG had antiviral properties, but said he also was aware at that time that 2'-CDG had been linked to toxicity issues. (Tr. 536:11-15; 550:20-551:5) However, Dr. Zahler could not recall how it was that he had learned that 2'-CDG was a "toxic" compound by this time. (Tr. 537:1-7; 551:6-11)

207. Dr. Zahler did not have any specific memory of the '244 Patent application, or of being asked for prior art with respect to that application. (Tr. 843:21-844:8) However, likely because he did not consider 2'-CDG to be pertinent to the discovery of entecavir, Dr. Zahler did not think about 2'-CDG during the prosecution of what became the '244 Patent. (Tr. 869:3-6) He did not make a deliberate decision to withhold information about 2'-CDG to the PTO during that prosecution. (Tr. 869:7-11)

208. During the time that the '244 Patent application was pending, from October 1990

through April 1993, Dr. Zahler believed the use of the exocyclic methylene group to be the most important feature of entecavir's structure. (Tr. 846:15-849:11) For this reason, BMS cited to Madhavan compound 30 as the most relevant piece of prior art in that application, a fact that was consistent with Dr. Zahler's understanding as to what was most important about his invention (since compound 30 contained an exocyclic methylene at the 5 prime (or 6 prime) position). (Tr. 849:12-850:5; 881:10-19) Madhavan was the only piece of art at the time that referenced an exocyclic methylene group at that position. (Tr. 308:13-309:1; 881:16-18)

209. As discussed above, 2'-CDG lacks the exocyclic methylene group required in every molecule claimed in the '244 Patent. (Tr. 936:20-22; DTX 126.002; JTX 1.0028) At the time of the '244 Patent application, Dr. Zahler was aware that 2'-CDG had structural similarities with entecavir, though he also was aware of what he described as differences between the two compounds—specifically that entecavir contained the double bond to carbon at the 5 prime position. (Tr. 544:6-546:14) Although 2'-CDG did not help him create the idea for entecavir, Dr. Zahler today acknowledges that in retrospect, he could see "decisions going either way," depending on how "broad you want to draw that circle [as to relevant prior art]," as to whether prior art disclosing 2'-CDG would be relevant and material prior art to the '244 Patent. (Tr. 546:15-547:21; 619:12-621:11)

210. Dr. Zahler could not be sure when he first became aware of the 1984 Shealy article, but the information in that article regarding 2'-CDG's excellent activity and high potency against HSV-1 and HSV-2 is consistent with what he knew about 2'-CDG at the time of his work on entecavir. (Tr. 537:1-541:12) Similarly, Dr. Zahler also knew of the Shealy '255 Patent at the time he came up with his idea for entecavir. (Tr. 548:10-16)

2. Stephen Venetianer

211. Mr. Venetianer was a patent prosecuting attorney at BMS from 1980 until December 1990. (Tr. 977:6-15) When he worked at BMS, Mr. Venetianer worked on patent applications regarding antiviral compounds, including the '244 Patent application. (Tr. 715:22-716:5; 732:16-733:15)

212. In working on such an application, he would consult with the inventor; in situations where the inventor had worked in the area for a while and had worked on other patent applications, he would ask the inventor to provide any relevant or close prior art to the invention. (Tr. 716:10-23; 733:16-24) Mr. Venetianer would explain to such inventors that it was incumbent upon them to tell him about prior art. (Tr. 735:13-16)

213. In deciding whether a piece of prior art was relevant to a patent application, Mr. Venetianer would consider whether the compound-at-issue was "structurally similar" to the compound referenced in the prior art. (Tr. 719:3-6) After meeting with an inventor (such as Dr. Zahler), Mr. Venetianer would prepare an application, send it to the inventor and review the draft with the inventor. (Tr. 736:12-14) If a rejection from the PTO was later received, he would meet with the inventor (including Dr. Zahler, if Dr. Zahler was the inventor) to discuss the rejection. (Tr. 736:15-24)

214. Mr. Venetianer believes there are similarities between the structures of 2'-CDG and entecavir, and that the only difference between them was that entecavir has a exocyclic methylene group on the five-membered ring, while 2'-CDG does not. (Tr. 718:2-11) However, as of the time of his deposition in this case, he could not state that the two compounds were

"structurally similar" without knowing more about the entire history and content of the compounds. (Tr. 718:12-20)

215. Mr. Venetianer was at least aware of the existence of the 1984 Shealy article and the Shealy '255 Patent, prior to submitting the application that led to the '244 Patent. For example, he disclosed the 1984 Shealy article and the Shealy '255 Patent by listing them on information disclosure statements during prosecution of another unrelated BMS patent application—U.S. Patent Application 07/286,914 ("the '914 application"), which later matured into U.S. Patent No. 4,918,075 ("the '075 Patent"). (Tr. 719:15-721:17; 724:12-725:11) Mr. Venetianer filed the '914 application, on which Dr. Zahler was a listed inventor, in December 1988. (DTX 163.0001; Tr. 721:18-722:6) Other than recalling that he must have considered the 1984 Shealy article and Shealy '255 Patent as prior art related to the '075 Patent, Mr. Venetianer had no recollection as to why he submitted these references to the PTO. (Tr. 725:12-24)

216. In January 1989, during Mr. Venetianer's work with the prosecution of another U.S. Patent Application 01/753,376 ("the '376 application") on which Dr. Zahler was a named inventor, the Examiner rejected certain claims as obvious in light of Marquez. (DTX 159.0063-.0065; DTX 160.0001-.0005)

217. Additionally, Mr. Venetianer disclosed Marquez in U.S. Patent Application 07/322,375 ("the '375 application). After the PTO rejected certain claims as to the '375 application as obvious in light of Marquez, Mr Venetianer responded to the PTO by noting that the compounds disclosed by Marquez had "antiviral activity." (DTX 2.0001, .0088, .0090, .0167 (reference J); DTX 164.0001, .0005; DTX 165.0005-.0007)

218. Mr. Venetianer also worked on U.S. Patent Application 07/546,957 ("the '957

application") while at BMS, an invention related to purinyl and pyrimidinyl tetrahydrofurans. (Tr. 727:1-23) Dr. Zahler was also a named inventor on this application. (Tr. 728:6-10) During that prosecution, the PTO Examiner issued an office action on November 30, 1990, in which she rejected certain claims as obvious over certain prior art, including the Shealy '255 Patent. (DTX 167.0008; Tr. 728:11-730:20) The Examiner, in her rejection, noted that certain secondary references (including the Shealy '255 Patent, which she did not mention by name) "teach antiviral activity for the deoxynucleosides, the isonucleosides and the carbocyclic analogs," such that a person of skill in the art would reasonably expect the claimed compounds and compositions to be useful for the same purposes. (DTX 167.0005) Upon receiving this rejection, Mr. Venetianer would have reviewed the Shealy '255 Patent. (Tr. 730:21-731:1) Just days later, in December 1990, Mr. Venetianer left BMS. (Tr. 977:15)

219. While at BMS, Mr. Venetianer worked on the '568 application, the first application that led to the '244 Patent. (Tr. 732:16-733:15) Looking back, as of the time of his deposition, Mr. Venetianer had no understanding as to whether 2'-CDG was disclosed to the PTO in this application or otherwise during the prosecution of what became the '244 Patent, nor was he able to form an opinion on whether 2'-CDG should have been disclosed to the PTO during that prosecution. (Tr. 726:6-24; 732:2-14; 977:22-978:20) He could not recall what his thought process was regarding the submission of the '568 application, nor why none of the references-at-issue were not cited to the PTO as part of that application, other than to say that BMS generally tried to cite all of the relevant prior art to the PTO. (Tr. 979:12-980:22)

220. As to his work on the '568 application, Mr. Venetianer recalled meeting with Dr.

Zahler prior to submitting the application. (Tr. 734:5-14) Along with the filing of that application, Mr. Venetianer filed an Information Disclosure Statement on October 12, 1990, which identified the prior art that the applicants believed "may be material to the examination of this application and in respect of which there may be a duty to disclose." (JTX 2.0107) That disclosure statement stated that "[a]ll of the attached references disclose antiviral compounds with exocyclic methylene double bonds. Applicants believe that Reference AX is the most relevant. Specifically, the Examiner's attention is directed to Compound 30 in the reference. . . ." (*Id.*) Reference AX was Madhavan, and Mr. Venetianer provided a copy of that reference to the PTO with the Information Disclosure Statement. (JTX 2.0127, .0156-.0062)

221. At the time of his deposition, Mr. Venetianer could not recall any specific discussion with the inventors of the '244 Patent about why the application cited Madhavan as the most relevant piece of prior art, nor about why that reference was included in the application, though he guessed that the inclusion of the reference came out of discussion with the inventors. (Tr. 737:14-738:19; 739:7-11; 981:13-21) He thought that structural similarities between Madhavan and entecavir related to why the inventors chose to include Madhavan in the application. (Tr. 738:20-739:2; 928:6-15; 981:22-982:3)

3. Stephen Davis

222. Mr. Davis was a prosecuting attorney at BMS from 1973 until 2005, during which time he prosecuted several applications pertaining to nucleoside analogs. (Tr. 674:9-20; 688:1-8; 915:23-916:5) Prior to his work at BMS, Mr. Davis had been a Patent Examiner at the PTO. (Tr. 675:2-6; 914:7-14)

223. At the time he prosecuted patents at BMS, he understood the importance of the

duty of candor to the PTO, including the duty to disclose material information regarding a patent application. (Tr. 675:7-15; 915:11-16) One way that Mr. Davis learned of material information with regard to patent applications was to meet with the inventors, in order to ask them what was relevant prior art. (Tr. 711:12-712:5)

224. Mr. Davis knew that if he were to be found to have committed inequitable conduct before the PTO while at BMS, this would invalidate the patent-at-issue, and that it could lead to his disbarment before the PTO and the termination of his employment at BMS. (Tr. 944:20-945:6) He did not make a deliberate decision to withhold any references from the PTO with regard to the '244 Patent application, as it would not "make sense to do so," because such references were public information that would eventually come to light. (Tr. 945:7-23)

225. Mr. Davis took over the prosecution of the '244 Patent from Mr. Venetianer, after Mr. Venetianer left BMS in December 1990, at a time when the '568 application was pending. (Tr. 676:12-677:8) This occurred because when Mr. Venetianer left BMS, Mr. Davis took over applications regarding approximately 10 patent families from Mr. Venetianer, including the '568 application. (Tr. 924:10-24; 926:1-5) These were the first cases in the antiviral and nucleoside areas that Mr. Davis had ever worked on, and, as a result, he slowly learned more about the applications over time. (Tr. 925:1-24)

226. Mr. Davis prosecuted the '244 Patent from the time he inherited the file from Mr. Venetianer onward, including the submission of an additional application, the '033 application, which ultimately matured into the '244 Patent. (Tr. 677:12-678:23) During the prosecution of the '244 Patent, Mr. Davis met with the inventors many times, and asked them for their prior art. (Tr. 712:10-18) At the time, the prosecution of the '244 Patent application was a "middle

priority" at BMS, not a "high priority," because BMS had not identified an agent in that family that was likely to be a commercial success. (Tr. 923:9-18)

227. Eventually, Mr. Davis filed the '033 application as a continuation-in-part application to the '568 application. (Tr. 676:12-677:2) He also filed another Information Disclosure Statement on September 17, 1991, in which he cited all of the references that had been cited in the prosecution of the earlier '568 application. (JTX 3.0118-0122) This disclosure stated that it included what Mr. Davis believed to be "the most relevant art." (JTX 3.0018)

228. On July 14, 1992, the Examiner issued an Office Action in the '033 application, rejecting the claims under 35 U.S.C. § 102(a) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a), as obvious over, a piece of prior art known as the "EP '849" application. (Tr. 678:24-681:23; JTX 3.0068-.0095, .0330-.0034) The Examiner cited the EP '849 application as an example of a compound having an exocyclic methylene group, and asserted that the claims of the '033 application were taught by the EP '849 application and were obvious in view of their "structural similarity." (Tr. 681:24-683:7; JTX 3.0333)

229. In response to that Office Action, Mr. Davis argued, *inter alia*, that the Examiner's interpretation of the EP '849 application was incorrect, because (1) the EP '849 application did not disclose an exocyclic methylene group on a cyclopentyl ring; (2) the Examiner had failed to suggest why a person of ordinary skill in the art would be motivated to replace or modify the cyclopentyl ring of the EP '849 application so as to arrive at the cyclopentyl ring of the instant claims and how that modification would be achieved; and (3) he had submitted a Rule 131 Declaration stating that the claimed invention was made in the United States before the May 2, 1990 publication of the EP '849 application. (Tr. 681:24-686:20; JTX 3.0340-.0042)

The Examiner later allowed the '244 Patent to issue; in doing so, the Examiner did not state which of Mr. Davis's arguments had motivated her to eliminate the EP '849 application as a reference that rendered the claims obvious. (Tr. 681:24-686:20)

230. Mr. Davis cited certain of the 2'-CDG prior art references-at-issue as part of his work on other BMS patent prosecutions. For example, on February 8, 1991, Mr. Davis filed U.S. Patent Application 07/652,823 ("the '823 application"), an application unrelated to the '244 Patent, on which Dr. Zahler and Dr. Slusarchyk were listed inventors. (Tr. 688:20-691:13) In the '823 application, Mr. Davis disclosed the Shealy 1984 article and Marquez to the PTO, and thus, he knew about these articles. (Tr. 691:20-694:19; DTX 4.0420, .0422, .0437, .0438) In addition, a copy of the Shealy '255 Patent was contained in the file history of the '823 application. (Tr. 695:19-696:11)

231. At the same time as he prosecuted the '244 Patent application, Mr. Davis also prosecuted two other patent applications on which Dr. Zahler was listed as an inventor: the '957 application (which Mr. Venetianer had also worked on) and U.S. Patent Application 07/656,391 ("the '391 application"). As previously noted, with respect to the '957 application, in November 1990, the Examiner had issued an office action in which she rejected certain claims as obvious over certain prior art, including the Shealy '255 Patent. (DTX 167.0005-.0008) Mr. Davis later tried to distinguish the Shealy '255 Patent to the Examiner, but acknowledged in doing so that the patent disclosed carbocyclic analogs with antiviral activity. (DTX 168.0001, .0012) With respect to the '391 application, in 1991, Mr. Davis listed Shealy 1984 and Marquez to the PTO as being relevant prior art. (DTX 5.0431, .0457, .0469, .0473)

232. With respect to the differences between 2'-CDG and entecavir, Mr. Davis believes

that the structural difference between the two is the addition of the exocyclic methylene group on the five-membered carbon ring in entecavir. (Tr. 697:18-698:4) He acknowledges that the structure of 2'-CDG and entecavir have similarities. (Tr. 698:5-10)

233. However, while Mr. Davis knew of 2'-CDG's existence, he was prosecuting applications regarding approximately 60 patent families (U.S. and foreign applications) at the time of the '244 Patent application. (Tr. 699:19-23; Tr. 711:11; 918:3-17) On any given day during this time, he would deal with a number of patent families. (Tr. 920:11-15) When working on a file of one of the 60 families, Mr. Davis tended to focus on that case, not all 60 cases at once (although at times, he would find overlap from one case to another). (Tr. 921:12-21) Once he finished working on one case and moved on to another, it could be months before he picked up work on the first case again. (Tr. 921:22-922:16)

234. As previously noted, Mr. Davis had knowledge of 2'-CDG during the time of the prosecution of the '244 Patent, in the sense that he knew of 2'-CDG's existence because he had worked on other patent prosecutions (like the '823 application) in which he had cited prior art referencing 2'-CDG to the PTO. (Tr. 700:1-10)

235. However, the reason Mr. Davis did not disclose 2'-CDG to the PTO during the prosecution of the '244 Patent was because he was not thinking of 2'-CDG at that time and because 2'-CDG was "not in front of" him during the '244 Patent prosecution. (Tr. 700:5-6; 701:22-703:17) Thus, Mr. Davis did not make a "deliberate decision" to not cite 2'-CDG to the PTO, as he did not, for example, look at the 1984 Shealy article and say, "no, I'd better not cite that." (Tr. 704:20-705:4; *see also* Tr. 711:2-11)

236. Had Mr. Davis instead been thinking of 2'-CDG in relation to the '244 Patent

application, he would have cited it to the PTO, because it "costs nothing to cite something to the Patent Examiner," and in doing so, he would have been strengthening the patent by citing whatever could be of relevance to the Examiner. (Tr. 702:12-22) Thus, if someone like the inventors had simply told him that 2'-CDG was relevant to the '244 Patent application, Mr. Davis "would have" cited the references to 2'-CDG. (Tr. 702:6-22; 713:5-9) This is because 2'-CDG had a "a five-membered ring and it has the hydroxy methyl and the hydroxy group on it," like entecavir did. (Tr. 703:3-5)

237. However, Mr. Davis also believes that there was more relevant prior art to the '244 Patent application, as compared to the references-at-issue that disclose 2'-CDG. (Tr. 703:7-11; 705:5-13) He agrees that when discussing an example of "closer" prior art, this refers to prior art related to compounds that are more similar to entecavir. (Tr. 705:17-21) Madhavan was cited by Mr. Davis in the prosecution history of the '244 Patent, and Mr. Davis today believes that it was more relevant prior art than the references-at-issue would have been. (Tr. 707:18-708:20; 932:1-9) This is because compound 30 in Madhavan shows the exocyclic methylene group on the cyclopentyl ring, (Tr. 708:14-20; 932:6-9), and Mr. Davis believes that the most important structural feature of the claims of the '244 Patent was the existence of the exomethylene group on the cyclopentyl ring. (Tr. 926:9-928:21; 932:1-9)

238. Mr. Davis does acknowledge that when comparing Madhavan's compound 30 to entecavir, there are three structural differences between them—two on the base of the compounds and one on the five-membered ring. (Tr. 709:12-22) In contrast, he notes that there is only one structural difference between 2'-CDG and entecavir—the addition of the exocyclic methylene group on entecavir's five-membered ring. (Tr. 710:17-20)

DISCUSSION

The discussion below begins with obviousness, as the Court discusses the selection of 2'-CDG as a lead compound and the skilled artisan's motivation to combine prior art references to arrive at entecavir with a reasonable expectation of success. The Court also addresses objective considerations of nonobviousness. After doing so, the Court ultimately concludes that Teva has proven by clear and convincing evidence that entecavir, claim 8 of the '244 Patent, would have been obvious within the meaning of Section 103 to a person of ordinary skill in the art as of October 18, 1990. Finally, the Court reviews and ultimately rejects Teva's allegations of inequitable conduct.

I. OBVIOUSNESS

A. Legal Standard

Under the United States Patent Act, an invention cannot be patented "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); *see also Galderma Labs., L.P. v. Tolmar, Inc.*, --- F. Supp. 2d ---, 2012 WL 4169686, at *44 (D. Del. Sept. 11, 2012). A patent granted by the PTO is presumed to be valid. 35 U.S.C. § 282(a); *see also Solvay, S.A. v. Honeywell Int'l Inc.*, --- F. Supp. 2d ---, 2012 WL 3561617, at *3 (D. Del. Aug. 20, 2012). The rationale underlying this presumption of validity is that "the PTO, in its expertise, has approved the claim . . . ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 426 (2007). The burden of proving invalidity rests with the patent challenger at all times, who must establish a patent's "obviousness by facts supported by clear and convincing evidence" in order to prevail.

Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963, 968 (Fed. Cir. 2006)[11]; *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1078 (Fed. Cir. 2012); *Solvay*, 2012 WL 3561617, at *8. Clear and convincing evidence places within the mind of the fact finder "'an abiding conviction that the truth of [the] factual contentions are highly probable.'" *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

With regard to the presumption of validity afforded to patents, however, the rationale underlying that presumption becomes "much diminished" if the PTO did not consider all of the material prior art references during prosecution of the patent. *KSR*, 550 U.S. at 426. In other words, "if the PTO did not have all material facts before it [during prosecution of the patent], its considered judgment may lose significant force." *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S.Ct. 2238, 2251 (2011) (citing *KSR*, 550 U.S. at 426). "And, concomitantly, the challenger's burden to persuade [the fact-finder] of its invalidity defense by clear and convincing evidence may be easier to sustain." *Id.* at 2251.

Generally, a party seeking to invalidate a patent as obvious must demonstrate "'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.'" *Procter & Gamble Co.*, 566 F.3d at 994 (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)); *see also Amgen Inc. v. F. Hoffman–La Roche Ltd*, 580 F.3d 1340, 1362 (Fed. Cir. 2009). The United

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[11] Because Federal Circuit precedent applies to issues unique to patent law, the Court will apply the law of the Federal Circuit to its obviousness and inequitable conduct analyses. *Alcon Research Ltd. v. Barr Labs. Inc.*, 837 F. Supp. 2d 364, 371 (D. Del. 2011).

States Supreme Court has emphasized, however, that the overall obviousness inquiry is "expansive and flexible." *KSR*, 550 U.S. at 415, 419; *see also OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 707 (Fed. Cir. 2012). In determining what would have been obvious to one of ordinary skill in the art, the use of hindsight is not permitted. *See KSR*, 550 U.S. at 421 (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning" in assessing obviousness); *see also Pfizer Inc. v. Teva Pharm. U.S.A., Inc.*, — F. Supp. 2d —, 2012 WL 2951367, at *13 (D. Del. July 19, 2012). Put another way, the task of determining whether a patent is invalid requires a court to "step back in time to before the moment of actual invention, and out of the actual inventor's shoes into those of a hypothetical, ordinary skilled person who has never seen the invention." *Eisai Co., Ltd. v. Teva Pharm. USA, Inc.*, No. 03 Civ. 9223(GEL), 2006 WL 2872615, at *2 (S.D.N.Y. Oct. 6, 2006) (citing *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983)).

Obviousness is a question of law that is predicated on several factual inquiries. *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966); *see also Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010); *Galderma Labs.*, 2012 WL 4169686, at *44. Specifically, the finder of fact must assess the following considerations: (1) the level of ordinary skill in the pertinent art; (2) the scope and content of the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective considerations of nonobviousness (sometimes referred to as "secondary considerations" of nonobviousness) such as commercial success, long-felt but unmet needs, and the failure of others (collectively, the "*Graham* factors"). *Graham*, 383 U.S. at 17–18; *see also Matrix Labs.*, 619 F.3d at 1352; *Galderma Labs.*, 2012 WL 4169686, at *44.

When the invention at issue is a chemical compound, "a *prima facie* case of obviousness under the third Graham factor frequently turns on the structural similarities and differences between the compound[] claimed and those in the prior art." *Matrix Labs.*, 619 F.3d at 1352 (citing *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (*en banc*) ("This court . . . reaffirms that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness.")); *see also Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356–57 (Fed. Cir. 2008). The determination of whether a claimed chemical compound would have been *prima facie* obvious over prior art compounds generally follows a two-part inquiry. *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). "First, the court determines whether a chemist of ordinary skill would have selected the asserted prior art compound[] as [a] lead compound[], or starting point[], for further development efforts." *Id.*; *see also Eisai Co.*, 533 F.3d at 1359. Second, the court determines "whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka*, 678 F.3d at 1292.

The Court should also, as part of its analysis of all of the evidence on the question of obviousness, consider evidence regarding objective considerations of nonobviousness. *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1075. An analysis of objective considerations of nonobviousness may not be deferred until after the fact finder makes an obviousness finding, nor should a fact-finder shift the burden of proof at any point (including when considering evidence of objective considerations) to the patentee; instead, at all times, the party challenging the patent

bears that burden, and must prove by clear and convincing evidence that the claim-at-issue of the patent is invalid. *Id.* at 1075-79.

B. Discussion

The first *Graham* factor requires the Court to define the level of ordinary skill in the art, as obviousness is judged from the perspective of a hypothetical person of skill in the art at the time the invention was made. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985). Such an individual is presumed to be aware of all of the pertinent prior art, and is "presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights." *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985); *see also Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000). In determining the level of ordinary skill in the art, a court may consider factors including: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field. *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007). As was set forth *supra* in Section II.C of the "Findings of Fact" section of this Memorandum Opinion, after taking into account evidence regarding a number of these factors, the Court has defined a person of ordinary skill in the relevant art as a medicinal chemist who could apply the tools of organic chemistry to design and make compounds, and who either (1) had a Ph.D. in organic chemistry or in medicinal chemistry and had been working for two or three years as a medicinal chemist; or (2) had a bachelor's

degree or master's degree in organic or medicinal chemistry and had been working in the field for 10–15 years.

As to the second and third of the *Graham* factors—regarding the scope and content of the prior art and the differences between the claimed invention and the prior art—the Court will analyze these factual considerations below in reviewing Teva's assertion that it has set out a *prima facie* case of obviousness. In putting forward its evidence in this regard, Teva contends that certain prior art (including Marquez, Shealy 1984, the Shealy '255 Patent, Montgomery 1989, and the 1989 Price article), would have motivated the chemist of ordinary skill in the art to select 2'-CDG as a lead compound. (*See* D.I. 151, 157) Upon selection of 2'-CDG, Teva argues that this chemist would then have pursued a finite number of obvious modifications, including one that would have resulted in entecavir: the addition of a single carbon atom at 2'-CDG's 5 prime position. (*See id.*) Furthermore, in light of the structural similarity between 2'-CDG and entecavir and the fact that this modification was made to other similar compounds and yielded antiviral activity, Teva asserts that the chemist would have reasonably expected entecavir to demonstrate antiviral activity and would have reasonably expected success in synthesizing the compound. (*See* D.I. 151, 157)

These inquiries must be examined as of "the time the invention was made." 35 U.S.C. § 103; *see also Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 536 F. Supp. 2d 476, 490 (D. Del. 2008), *aff'd*, 566 F.3d 989 (Fed Cir. 2009). The date of invention is "presumed to be the filing date of the parent application." *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000); *Procter & Gamble Co.*, 536 F. Supp. 2d at 490. However, this presumption can be rebutted by showing either an earlier reduction to practice or an earlier

conception and diligence in reduction to practice. *Procter & Gamble Co.*, 536 F. Supp. 2d at 490 (citing *Price v. Symsek*, 988 F.2d 1187, 1190 (Fed. Cir. 1993)). The burden is on the party asserting an earlier invention date to rebut this presumption by a preponderance of the evidence. *Id.* Here, in arguing that its cited references qualify as prior art, Teva notes that the date of invention should be "deemed to be the date of filing of the patent application" "unless BMS proves otherwise." (D.I. 151 at 6) For its part, BMS does not appear to argue for an earlier date of invention. For instance, BMS does not quarrel with the dates of Teva's cited prior art references except to argue that Teva's expert, Dr. Heathcock, improperly failed to consider the full scope of the prior art when giving his obviousness opinion (including a failure to consider references dealing with furanose and acyclic analogs). (D.I. 150 at 17-24) Thus, because BMS puts forward no arguments regarding an earlier date of invention, the Court will presume that the date of filing of the parent application, October 18, 1990, is the date of the invention.

1. Teva's *Prima Facie* Case

a. It Would Have Been Obvious to Select 2'-CDG as a Lead Compound.

To prevail on the theory that entecavir was an obvious modification of 2'-CDG, Teva must first establish by clear and convincing evidence that the chemist of ordinary skill in the art would have been motivated to select 2'-CDG as a lead compound in October 1990.

The Federal Circuit has defined a "lead compound" as "a compound in the prior art that would be most promising to modify in order to improve upon [that compound's activity] and obtain a compound with better activity." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007); *see also Otsuka*, 678 F.3d at 1291. Accordingly, a lead

compound is "a natural choice for further development efforts." *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009); *see also Otsuka*, 678 F.3d at 1291. Such a compound may be one of a number of compounds that the skilled artisan would have been motivated to select from the panoply of known compounds in the prior art, based on the lead compound's promising useful properties. *Otsuka*, 678 F.3d at 1292; *Matrix Labs.*, 619 F.3d at 1354; *Altana*, 566 F.3d at 1008.

Generally, a *prima facie* case of obviousness is premised upon, *inter alia*, structural similarity between the purported lead compound and the claimed compound, where the prior art gives reason or motivation to make the claimed composition, because "close or established '[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds.'" *Takeda*, 492 F.3d at 1356 (citing *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)). This is so because compounds with similar structures "'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.'" *Id.* at 1365 (citing *In re Deuel*, 51 F.3d at 1558).[12]

However, "[a]bsent a reason or motivation based on [] prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead

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[12] As was previously noted, this process—making modifications to a lead compound in the hopes of developing new compounds with improved pertinent properties—is known as structure-activity relationship testing. *See supra* ¶ 30; *Pfizer Inc. v. IVAX Pharm., Inc.*, Civil Action No. 07-CV-00174 (DMC), 2010 WL 339042, at *3 (D.N.J. Jan. 20, 2010) (noting that the inventors selected a lead compound, synthesized a variety of new compounds based on the lead compound's structure, conducted testing on those new compounds "to observe their pharmacological activities," and based on those results, experimented with other potential modifications to the lead compound which they then synthesized and tested—a process known as "structure-activity relationship testing").

compound selection." *Otsuka*, 678 F.3d at 1292. The court's analysis in considering whether a skilled artisan would have selected a prior art compound as a lead must then be "guided by evidence of the compound's pertinent properties." *Id.* These properties "may include positive attributes such as activity and potency . . . adverse effects such as toxicity, . . . and other relevant characteristics in evidence." *Id.* (citations omitted). In determining whether a particular compound would have been selected as a lead, "no one characteristic of the compound is necessarily dispositive." *Pfizer v. IVAX Pharm., Inc.*, Civil Action No. 07-CV-00174 (DMC), 2010 WL 339042, at *8 (D.N.J. Jan. 20, 2010). However, the court's analysis of whether a compound would have been a likely lead "must avoid hindsight bias." *Matrix Labs.*, 619 F.3d at 1354. That is, in such a case, the patent challenger must point to more than mere structural similarity as a reason to select a compound as a lead; "knowledge in the art of the functional properties and limitations of the prior art compounds" is also very important to the analysis. *Id.*

Here, the prior art clearly would have directed the skilled artisan to select 2'-CDG, a carbocyclic analog, as a lead compound for further development efforts as of October 1990. BMS argues to the contrary that the evidence "shows that numerous other lead compounds would have been more likely to have been chosen by a person of ordinary skill in the art" at this time. (D.I. 150 at 68) As an initial matter, it is worth noting that the Federal Circuit has rejected the notion that the "prior art must point to only a single lead compound for further development efforts." *Altana*, 566 F.3d at 1008. In other words, in the expansive field of nucleoside analogs, the Court need not identify a "single, best lead compound" in the prior art. *Matrix Labs.*, 619 F.3d at 1354. In this case, while BMS is correct that the two other categories of nucleoside analogs—furanosides and acyclics—had good antiherpetic track records by the 1980s, (D.I. 150

at 68), it is also true that during this time, medicinal chemists were actively exploring carbocyclic analogs as a fertile place to begin in quests to discover new drugs. While it is possible that the skilled artisan may have chosen other lead compounds from which to start, for the reasons set forth below, Teva has succeeded in "demonstrat[ing] by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select [2'-CDG] over other compounds in the prior art." *Matrix Labs.*, 619 F.3d at 1354.

(1) There was Excitement Surrounding Carbocyclic Nucleoside Analogs in the Late 1980s and 1990

The conclusion that a skilled artisan would have looked to 2'-CDG as a lead compound is first bolstered by the evidence showing that, as a class of nucleosides analogs, carbocyclic analogs had generated excitement in the late 1980s among researchers searching for compounds with antiviral activity. Dr. Heathcock noted this excitement. He opined that, as compared to the "crowded field" of acyclic nucleosides that had been "quite actively investigated" by the late 1980s, or the class of furanose analogs, where you "might have a hard time finding something someone else hadn't already tried," the carbocyclic nucleoside analog field was a "fertile" one for the development of new drugs. (Tr. 159:3-5; 168:19-24; 278:22-23)[13] Indeed, BMS's own

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[13] BMS spends several pages of its post-trial briefing arguing that Dr. Heathcock "erred as a matter of law" in opining about the obviousness of entecavir because his analysis "consider[ed] only 2'-CDG as a potential lead compound" while failing to consider furanosides or acyclics as potential leads. (D.I. 150 at 64–69) The Court does not agree with this description of Dr. Heathcock's analysis, because while he may not have reviewed "every single paper [or] every single patent" in the field, (Tr. 295:19), his testimony revealed that he did in fact take into account other areas of prior art and other potential lead compounds, including the classes of furanosides and acyclics. Dr. Heathcock identified, "based on [his] review of the prior art," three areas of nucleoside analogs that scientists had worked with: furanosides, acyclics and carbocyclics. (Tr. 158:11–19) He went on to explain these different classes, giving examples of compounds that had been developed in each. (Tr. 158:19–169:9) For instance, while BMS accused Dr. Heathcock of "ignor[ing] prior art regarding acyclic nucleoside analogs, including

expert, Dr. Schneller, conceded that by the 1980s, "[t]here was interest beginning to grow, of course" in the field of carbocyclic analogs. (Tr. 1154:5–9; *see also* 1155:4–7) In fact, Dr. Schneller pegged the interest in carbocyclics as beginning *two decades* earlier: "[the interest in carbocyclics] really started back in the sixties . . . the biological interest in carbocyclic nucleosides can be traced much farther back than the eighties." (*Id.* at 1154:10–23) Indeed, by 1991, Dr. Schneller and students in his laboratory worked almost exclusively on synthesizing carbocyclics, as he noted that was "most of what we did." (Tr. 1194:10-11)

BMS argues that the skilled artisan would have been more likely to choose an acyclic or furanose lead compound at this time, particularly an acyclic, as two compounds from that class (acyclovir and ganciclovir) had garnered FDA-approval (while no carbocyclic had yet been approved). (D.I. 150 at 68; *see also* D.I. 156 at 6) However, in 1989, *BMS itself* was touting the promise exhibited by carbocyclics. At a September 1989 conference, BMS specifically noted that the carbocyclic lobucavir, which Dr. Zahler had invented en route to conceiving of entecavir,

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references that would suggest acyclics as potential lead compounds," (D.I. 150 at 67), Dr. Heathcock pointed out during his discussion of acyclics that they "were actively investigated" and his slides relating to this field included examples that he "pulled . . . from a paper by Dr. Keller [who] reported several dozen [acyclic analogs]." (Tr. 162:24–163:2; *see also* JTX 68) BMS also accuses Dr. Heathcock of basing his analysis on "hindsight," apparently because he reviewed the '244 Patent first and from there used it as a "template." (D.I. 150 at 66 (citing Tr. 287:6-12)) But Dr. Heathcock was required to look at the patent in order to assess "the differences between the prior art and the claims at issue," *Graham*, 383 U.S. at 17, and, as previously noted, the full measure of his testimony does not support the claim that he focused on 2'-CDG to the exclusion of other compounds or classes of compounds. Additionally, BMS claims that in two prior cases, this Court has "found Dr. Heathcock's application of the same methodology to constitute 'hindsight' and provide no credible evidence." (D.I. 150 at 63, 65–66) The Court does not read either of those cases to have involved an adverse finding regarding Dr. Heathcock's personal credibility, nor does it find his testimony in those cases relevant to the instant matter. Ultimately, as is more fully set forth below, it is difficult for BMS to persuasively attack the content of Dr. Heathcock's testimony, when BMS's own expert, Dr. Schneller, agreed with Dr. Heathcock on many important points constituting Teva's lead compound analysis.

"is superior to acyclovir, and comparable to ganciclovir"—the very two compounds that BMS specifically calls out in its post-trial briefing as more promising lead compounds than 2'-CDG—against the herpes viruses and various other viruses. (*Compare* D.I. 150 at 68-69, *with* PTX 445.0003) And while BMS characterizes Dr. Zahler's initial drug discovery quest as "a perfect test case for which lead compound a person of ordinary skill in the art would choose," noting that he had first selected acyclovir as a lead compound to work with, (D.I. 150 at 69–70), this glosses over the fact that Dr. Zahler's selection of acyclovir occurred in 1986. By 1990—the relevant time frame here—even Dr. Zahler had turned to the fertile field of carbocyclics, beginning with his invention of lobucavir.[14] Thus, in 1989—decades before this litigation (and thus well before BMS's current claim that "in 1989, there were substantial reasons to avoid carbocyclic nucleoside analogs generally"), (D.I. 150 at 70)—*BMS* had praised lobucavir, a carbocyclic, as superior to acyclovir and comparable to ganciclovir. This further illustrates that carbocyclics were "a natural choice for further development" at this time.

BMS was not alone in recognizing the promise exhibited by carbocyclics. In the wake of Dr. Shealy's work with these nucleosides at SRI, many other researchers were doing the same. The Marquez article, published in 1986, concluded that "good antiviral activity appeared to be the rule rather than the exception among carbocyclic nucleosides." (DTX 171.0038) The Biggadike article, published in 1987, noted the "considerable current interest in the synthesis of

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[14] *Cf. Altana Pharma AG v. Teva Pharm. USA, Inc.*, 532 F. Supp. 2d 666, 677 (D.N.J. 2007), *aff'd*, 566 F.3d 999 (Fed. Cir. 2009) (rejecting plaintiff's argument that the first FDA-approved drug in the field was the "gold standard" for further development and thus would have been selected over defendants' asserted lead compound during the relevant time frame, where plaintiffs' own statements at the time of the invention indicated that its own non-FDA-approved compound was then a "significant improvement[]" over the FDA-approved compound).

carbocyclic nucleosides" because of the significant antiviral activity displayed by some such compounds. (DTX 150) The Madhavan article, published in 1988, discussed the Syntex laboratory's work developing carbocyclic nucleoside analogs and analyzing the antiviral activity of such analogs. (JTX 81) And the Montgomery 1989 review article called out carbocyclic nucleoside analogs as "[b]y far the most active and selective agents" among the compounds identified by SRI with promising antiviral activity, (DTX 172.0004)—a finding Dr. Heathcock called an "open invitation" to medicinal chemists to "look at that class of compounds as leads," (Tr. 188:8-189:15).

Accordingly, then, the prior art in the relevant time period clearly pointed the skilled artisan to carbocyclics as a promising area for drug discovery.

(2) The Person of Ordinary Skill in the Art Would Have Selected 2'-CDG as a Lead Compound.

Furthermore, beyond the promise that carbocyclics as a class were showing during this time, the evidence clearly demonstrates that the skilled chemist examining the carbocyclics field as a starting point for drug discovery would have targeted 2'-CDG as a "natural choice for further development." *Altana*, 532 F. Supp. 2d at 677. Indeed, medicinal chemists during the relevant time frame *were actually treating and using* 2'-CDG as a lead compound; it is hard to conceive of more powerful evidence for this prong of the lead compound analysis. As BMS itself states, "it is not sufficient that a potential lead compound would be a good option, it must be a better option than the alternatives." (D.I. 150 at 67) By many accounts, 2'-CDG was indeed recognized as that better option.

(a) Structural Similarity Between 2'-CDG and Entecavir

While it is not the only factor guiding the first prong of the lead compound analysis (whether the skilled artisan would have selected 2'-CDG as a lead compound), structural similarity may be considered along with the prior art compound's other pertinent properties. *See, e.g., Matrix Labs.*, 619 F.3d at 1354 ("[P]roving a reason to select a compound as a lead compound depends on more than just structural similarity . . . ."); *see also Otsuka*, 678 F.3d at 1292 ("Absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection."); *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997) ("Structural relationships often provide the requisite motivation to modify known compounds to obtain new compounds.").

It is clear that 2'-CDG and entecavir would have been deemed by a person of skill in the art to be, as Dr. Heathcock opined, "structurally very similar." (Tr. 220:7-8) While 2'-CDG has a single carbon atom at the 5 prime position, entecavir has an exocyclic methylene group (a carbon-carbon double bond) at that position. (Tr. 220:2-8) In other words, the *only* structural difference between the two compounds is the addition of a single carbon atom at the 5 prime position of the ribose portion of entecavir. (*Id.*) BMS itself acknowledges that "[a]t a high level, [entecavir and 2'-CDG] do share structural similarities: they all have guanine bases, they all lack 2' hydroxyl groups, and they all have 4' hydroxymethyl groups." (D.I. 156 at 7 n.3)[15]

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[15] This acknowledgment is similar in kind to the trial testimony of Dr. Zahler and Mr. Davis, in which both men acknowledged that 2'-CDG could be viewed as structurally similar to entecavir (though they also noted that in their view, *inter alia*, the addition of the exocyclic methylene group in entecavir amounted to a significant structural difference between the compounds). Dr. Zahler, for example, noted that while the two compounds have "some structural similarity[,] they also have some very significant differences." (Tr. 547:14-17; *see also* 608:16-19 (noting that the two compounds are "structurally similar and dissimilar")) Mr. Davis, for his part, acknowledged that while the two compounds are not identical, they "have similarities." (Tr. 698:5-10) He explained that these similarities were significant enough that

It would be difficult for BMS to convincingly assert otherwise, since BMS's own pre-litigation publications and computer modeling experiments support the conclusion that the two compounds are structurally similar. For example, a July 1997 article authored by a number of BMS scientists, including Dr. Zahler, referred to 2'-CDG as "structurally similar" to entecavir. More specifically, the article described 2'-CDG (in relation to entecavir) as "a structurally similar guanine-based nucleoside in which the natural furanose oxygen is also replaced by a carbon. . . ." (JTX 107.0003) In his trial testimony, Dr. Zahler first suggested that this reference only meant to assert that "like 2'[-]CDG, [entecavir] is a . . . carbocyclic nucleoside." (Tr. 613:19-20) When confronted on cross-examination with the fact that the article says more than that—that it focuses on the "structural similar[ity]" of the two compounds—Dr. Zahler then acknowledged that "[y]ou could read [the article] that way," but said that the words used in the article are "not my words" and were instead the words of the "primary authors" of the article that were used "loosely." (Tr. 614:18-23) He went on to again state that the compounds are also structurally different, though acknowledging that the article does not emphasize that difference. (Tr. 614:23-615:7)

The Court, having observed this testimony, did not find Dr. Zahler's reading of the article's meaning convincing. The article, written long before this litigation commenced, was emphasizing the undeniable structural similarities between the two compounds, not any differences between them. Dr. Zahler was an author of the article, and in that sense the words used in the article *are* both his words and the words of his fellow colleagues at BMS—words that

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had 2'-CDG been brought to his attention at the time of the '244 Patent application, he "would have" cited prior art referencing the compound to the PTO. (Tr. 703:3-6) This is because 2'-CDG had "a five-membered ring and it has the hydroxy methyl and the hydroxy group on it," like entecavir did. (*Id.*)

they transmitted to the scientific community and words that have import.[16] (Tr. 617:14-618:6 (Dr. Zahler noting that this article was meant to be "straightforward" in its descriptions, so that scientists could read and interpret its meaning)) The fact that BMS and Dr. Zahler, well before this case began, were emphasizing the structural similarities between 2'-CDG and entecavir (and not noting any differences between them) is persuasive evidence to the Court that those similarities are compelling.

Indeed, in another 1998 article authored by BMS scientists, BMS again reiterated the structural similarity between 2'-CDG, entecavir and lobucavir (another carbocyclic analog) in their triphosphate forms, noting that they are "structurally related." (JTX 108.0008) As with the 1997 article, this article did not mention any structural differences between the two compounds.

In addition to emphasizing the structural similarity of entecavir and 2'-CDG in its own literature, BMS also highlighted the structural similarity of the two compounds soon after Dr. Zahler conceived of entecavir. BMS's computer modeling of nucleoside analogs, performed around May 1989 under Dr. Zahler's direction, revealed that entecavir and 2'-CDG had similar three-dimensional conformations (or shapes)—since both conformations were in a "boundary" that BMS used to predict bioactivity. Notably, 2'-CDG was the "only non-BMS compound" utilized in the computer modeling. (Tr. 658:6–15); *cf Altana*, 566 F.3d at 1008 (noting that when a patent holder "itself had selected [the purported lead compound] for further development efforts," even though the inventor did not use the compound to create the patented invention, this

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[16] (*Cf.* D.I. 129 at 4 (District Court, in a pre-trial Memorandum Opinion, noting that as to the structural similarity between 2'-CDG and entecavir, Dr. Zahler "is one of several people credited with an article which contains a statement about 2'-CDG's 'structural similarity' to entecavir" but "said he had neither written nor read it before it was published" and concluding that this "at least raises a credibility concern" that should be further examined at trial)).

suggested that the purported lead compound was a "natural choice for further development efforts" at the time). The fact that BMS, at the time of the invention of entecavir, identified 2'-CDG as having a similar three-dimensional shape to entecavir—so similar that 2'-CDG was among a handful of compounds (and the only non-BMS compound) it used to help determine whether entecavir should be synthesized—is also powerful corroborating evidence of Dr. Heathcock's opinion regarding structural similarities between the compounds.

BMS nevertheless argues that there are differences between the three-dimensional structures of entecavir and 2'-CDG, due to the addition of the exocyclic methylene group in entecavir, and that these differences are among the reasons that the skilled artisan would have rejected 2'-CDG as a lead compound. (*See, e.g.*, D.I. 150 at 76 ("These structural differences [between entecavir and 2'-CDG] may seem small in a two-dimensional depiction, but in three dimensions (as they would be viewed by the person of ordinary skill), they are vitally important because they have huge ramifications for the function of the two molecules.")) As noted above, BMS's own computer modeling history suggests that significant three-dimensional similarities exist between the compounds. However, even acknowledging that there are some three-dimensional differences between the compounds, Dr. Zahler himself testified that many chemists *do not* analyze structural similarity between compounds by thinking in three dimensions.[17] (Tr. 886:12–19) This point is perhaps best emphasized by the fact that Dr. Zahler himself did not know the three dimensional structure of Madhavan 30, the compound presented to the PTO as

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[17] Indeed, at trial, Dr. Schneller emphasized that the fact that Dr. Zahler thought about the similarities and differences of compounds like entecavir in three dimensions, and used three-dimensional computer modeling to do so, made him a "pioneer" in rational drug design. (Tr. 1141:5-1145:2)

the closest prior art during prosecution of the '244 Patent. (Tr. 633:2-7) Instead, at that time, BMS pointed the PTO to Madhavan 30 as the most relevant piece of prior art, not because of any three-dimensional similarities (or differences) between those two compounds, but because of the two-dimensional similarities between the two. (Tr. 632:20-633:1) Therefore, the totality of the evidence shows that the ordinary medicinal chemist working in October 1990 to develop an antiviral compound would be largely focused on two-dimensional structural similarities between the compounds, which were also significant.[18]

For these reasons, the Court finds that 2'-CDG and entecavir would have been deemed to be structurally similar by a person of skill in the art in the relevant time period.

(3) Properties of 2'-CDG

In determining whether the skilled artisan would have selected 2'-CDG as a lead compound, its pertinent properties—including positive attributes like activity and potency, adverse effects such as toxicity issues, and other relevant characteristics—must be examined. *See, e.g.*, *Otsuka*, 678 F.3d at 1292.

Here, in the relevant time period, the prior art as a whole taught that 2'-CDG was a promising compound in the carbocyclics field because it had demonstrated very good antiherpes activity, high potency against HSV-2, and because it was more effective than Ara-A, an FDA-approved furanoside used to treat herpes. These positive attributes began to be called out soon

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[18] Thus, put another way, the person of skill would not likely have been thinking of three-dimensional similarities or differences at the relevant time, and in focusing on two-dimensional similarities, would have found the compounds to be structurally similar. The Court, now having reviewed evidence of BMS's own three-dimensional testing of the compounds at the time, finds that even though the person of skill in the art would not likely have been focused on three-dimensional similarities and differences, if they had, it only would have been further compelling evidence to support the conclusion of structural similarity.

after Dr. Shealy's invention of 2'-CDG, as the Shealy 1984 article noted that 2'-CDG had better *in vitro* activity against HSV-1 and HSV-2 than did Ara-A and noted the compound's high potency and excellent activity against these viruses. (Tr. 168:24-174:1, DTX 126.0002) The Shealy '255 Patent, issued in September 1985, disclosed the invention of a number of compounds, including 2'-CDG, and noted particularly that 2'-CDG was one of two compounds that was "markedly more effective" than Ara-A against HSV-1 and HSV-2. (Tr. 178:13-18; DTX 151.0008) The Marquez article (published in 1986) and the Shealy 1987 article both contain data further noting these positive results as to potency and activity regarding the herpes viruses. (DTX 171.0017; DTX 125.0002; Tr. 181:13-182:3) In November 1989, the Price article published the results of testing 2'-CDG against hepatitis B, noting that the compound showed excellent activity against that virus, results that would have highlighted 2'-CDG's "very good therapeutic window" in this regard. (DTX 152; Tr. 187:21-24) And in the Montgomery 1989 article, the authors cited the fact that 2'-CDG was five to six times as potent as acyclovir against HSV-1 and HSV-2 in certain testing—a "lamp post that really illuminat[ed]" 2'-CDG as a "very exciting lead compound to work from" at the time. (DTX 172.0016; Tr. 191:5-10)

The case law emphasizes that compounds called out in the prior art as exhibiting the highest potency and/or activity are the most likely leads.[19] BMS does not attempt to refute that

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[19] *See generally Otsuka*, 678 F.3d at 1294 (noting that "generally, a skilled artisan would be attracted to the most potent compounds in selecting a lead compound for development") (internal quotation marks and citations omitted); *see also Altana*, 566 F.3d at 1007–08 (affirming district court's denial of plaintiff's motion for preliminary injunction and citing as evidence that defendants raised a substantial argument that compound 12 would have been selected as a lead compound, in that "compound 12 was disclosed as one of the more potent of the eighteen compounds" in the prior art); *OSI Pharm., Inc. v. Mylan Pharm. Inc.*, 858 F. Supp. 2d 341, 356-57 (D. Del. 2012) (rejecting defendant's argument that example 51 would have been selected as a lead compound because, *inter alia*, there was better, more robust potency

2'-CDG's promising properties were being widely reported in the literature in the late 1980s, as indeed they were.

BMS, however, focuses heavily upon 2'-CDG's toxicity in contending that the skilled chemist would not have selected 2'-CDG as a lead compound. (*See, e.g.*, D.I. 150 at 71 ("[T]he clearest reason to avoid [2'-CDG] as a lead compound was its toxicity. Even Dr. Heathcock recognized that 2'-CDG is known to be toxic by those of skill in the art *today*.")) (emphasis added) The significant problem with BMS's argument is that, as of October 1990, 2'-CDG was *not yet known* to have a high toxicity. In support of its argument that the chemist would not have selected 2'-CDG as a lead compound because of its toxicity, BMS focuses on: (1) the results of Dr. Tennant's testing of 2'-CDG in the woodchuck model, performed in 1990 and 1991; (2) three articles published in 1992; and (3) purported indications of toxicity in Shealy 1984, Montgomery 1989, and the Bennett article.[20] (D.I. 150 at 71)

Dr. Tennant's testing of woodchucks did not occur until 1990 and 1991, and prior to his experiments he was "absolutely not aware" of any toxicity associated with 2'-CDG. (Tr. 1022:16–1023:6) Dr. Tennant explained that had he known that 2'-CDG was toxic, or if toxicity data regarding 2'-CDG was available during these time periods, he would have considered the

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data for other compounds; therefore, the court was not persuaded by defendant's argument because the skilled artisan "had several alternatives to consider and [] potency drives the research").

[20] In a footnote in its reply brief, (D.I. 156 at 6 n.2), BMS also points to an internal status report that noted that a proprietary nucleoside analog was abandoned because "its 'spectrum of activity and toxicity is similar to that found for'" 2'-CDG. (DTX 141.0006) However, while BMS refers to this as a 1990 report, there is no indication of when it was published; the document merely indicates that the period covered is June 1, 1990 through November 30, 1990. (*Id.*) But the publication date does not ultimately matter, because this internal document is not prior art under the law.

data and would not have administered the lethal doses of the compound that he did to his woodchuck colony. (Tr. 1022:16-1023:13) Indeed, Dr. Tennant's unpublished July 1991 report summarizing the testing, described the toxicity results as "unanticipated." (JTX 141.0007) Likewise, the 1992 articles that BMS cites post-date the October 1990 presumed invention date of the '244 Patent. In short, this evidence would not have deterred the skilled chemist from selecting 2'-CDG as a lead compound during the relevant time period because *it did not exist* at that time, and thus could not have been available to that chemist.

The purported indications of toxicity in Shealy 1984 (Table III), Montgomery 1989 (Table 6), and the Bennett article (which was published sometime in 1990, though the exact date of publication is unclear) are unclear or tentative at best. The Shealy 1984 article and Montgomery 1989 article, as noted above, focus almost exclusively on 2'-CDG's promising antiviral properties, and no part of the text of those articles highlights any concern regarding toxicity and 2'-CDG. *See supra* ¶¶ 87-89. As noted above, in attempting to argue that these articles highlighted such toxicity data, BMS points to two tables that do not show negative results in the portions of those tables that are focused on toxicity. *See id.*; (D.I. 150 at 71) As to the 1990 Bennett article, while it did make reference to some apparent cytotoxic effects of 2'-CDG, the article also highlighted how 2'-CDG has a "greater effect on the virus than . . . on the cell itself." (Tr. 374:2-10; JTX 90.0007) In his testimony at trial, Dr. Heathcock discussed each of these references, explaining why the language used in them would not steer the ordinary medicinal chemist away from selecting 2'-CDG as a lead compound. (Tr. 257:4–259:15; 267:18-

23; 373:9–374:18)[21] In contrast, the Court finds it notable that BMS's expert, Dr. Schneller, provided no trial testimony about references to toxicity in any of these three articles, nor that any such references would have deterred a person of ordinary skill in the art from selecting 2'-CDG as a lead compound.[22]

Even accepting BMS's strained reading of the toxicity indications in these few articles appearing before the close of 1990, the evidence of record does not suggest that such unclear indications would have steered the skilled artisan away from 2'-CDG. It is significant, for example, that Dr. Slusarchyk himself testified that at the time he was synthesizing entecavir, while toxicity data about nucleoside analogs that he was making would have been of interest to him, it "wouldn't deter [him] from making more compounds in the area to investigate further."[23] (Tr. 508:8–19) Toxicity data about a particular alleged lead compound in and of itself does not automatically render that compound incapable of being a lead. *See Altana*, 566 F.3d at 1008 (noting that "[a]lthough [plaintiff's] expert suggested that one of skill in the art would have

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[21] In fact, as to the Montgomery 1989 reference, when Dr. Heathcock was cross-examined about the reference at trial, he was not asked at all about the table that BMS, in its post-trial briefing, now suggests would have raised toxicity questions. (Tr. 269:7-272:9)

[22] It is also important to note that, even to the extent that there was some indication in these articles that 2'-CDG *may* have toxicity issues, they conflicted with other prior art in the time period that clearly indicated that 2'-CDG was *not* toxic (such as the 1989 Price article). *See Novartis Pharm. Corp. v. Teva Pharm. USA, Inc.*, Civil Action No. 05-CV-1887 (DMC), 2007 WL 2669338, at *7 (D.N.J. Sept. 6, 2007) (stating that "it is evident that the prior art produced some conflicting results about . . . the toxicity of [the prior art compound penciclovir]" and the article reporting some toxicity issues "should be weighed equally with the other prior art references" because "[t]here are far greater references teaching that penciclovir would act as a powerful antiviral agent").

[23] Relatedly, when the Madhavan group at Syntex discovered Madhavan 30 in 1988, it used aristeromycin as a lead compound—a carbocyclic analog known to have toxicity associated with it. (Tr. 212:8–16; 1240:13-24; JTX 81; DDX 61)

selected omeprazole over [compound 12], in part because of toxicity concerns, the district court apparently accepted Dr. Mitscher's contrary opinion [and such reliance on that opinion] was not clearly erroneous").

In light of all of the teachings in the prior art about 2'-CDG's pertinent properties, considered mostly excellent in 1990, speculative toxicity data would not have stopped the skilled chemist from choosing 2'-CDG as a lead compound at that time.[24]

Perhaps the best indication that any such tentative references to possible toxicity did not stop the medicinal chemist from selecting 2'-CDG as a lead compound in the late 1980s and 1990, in light of its positive benefits, is the fact that researchers were *actually treating and using* 2'-CDG as a lead compound during the relevant time period.[25] In its post trial briefing, BMS argues that Teva (and its expert Dr. Heathcock) are wrong in stating that other researchers,

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[24] BMS appears to also argue at one point that the Court must consider a compound's relevant properties in its obviousness analysis "whether they are known at the time of the invention or later," (D.I. 150 at 75), but the *prima facie* obviousness analysis is focused squarely on the time period in which the invention occurred. *See OSI Pharm., Inc.*, 858 F. Supp. 2d at 355 (explaining that "'the court must look at the state of the art *at the time the invention was made* to find a motivation to select [a lead compound]'") (emphasis in original) (quoting *Matrix Labs.*, 619 F.3d at 1354). The cases to which BMS cites in support of its argument are inapposite on this point, since they indicate that a court may consider later-discovered evidence in the context of evaluating an invention's *unexpected results*, which is an objective consideration of nonobviousness. *See Knoll Pharm. Co., Inc. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1384–85 (Fed. Cir. 2004) (noting that the district court refused to consider the plaintiff's unexpected results evidence because such results were discovered after the patent-in-suit was issued before stating that "later-obtained data" may be submitted in support of patent validity); *see also Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307–08 (Fed. Cir. 2011) (same).

[25] This fact also undercuts BMS's argument that the skilled artisan would have shied away from 2'-CDG as a lead compound (and in fact carbocyclics as a whole) because they were "relatively difficult to synthesize." (D.I. 150 at 70-71; *see also* D.I. 156 at 6)

including the researchers at SRI and Glaxo, were actually treating 2'-CDG as a lead compound at this time. (D.I. 150 at 71-74) Yet this argument flies in the face of the testimony from BMS's expert, Dr. Schneller, who repeatedly testified at trial that such chemists *were, in fact*, treating and using 2'-CDG as a lead compound during this time period. On cross-examination, after first noting that he did not "completely disagree" with Dr. Heathcock's opinion that 2'-CDG was a lead compound, (Tr. 1164:10-19), Dr. Schneller was asked and said the following:

Teva's counsel:	Now, actually, sir, where I think you agreed with Dr. Heathcock is that you would think about 2'-CDG as a lead compound back in that time period?
Dr. Schneller:	Back in that time period. I may not have, but apparently others did. . . . .
Teva's counsel:	But you acknowledge that there were people who were talented in this area who were treating 2'-CDG as a lead compound?
Dr. Schneller:	Yes, sir. . . .
Teva's counsel:	And you understand there were people in the art at the time in the eighties who said that 2'-CDG was a lead compound?
Dr. Schneller:	There were people that did that, yes, sir.

(Tr. 1164:15–19; 1166:3–15; 1167:4–10)

In its post-trial briefing, BMS argues that the 1987 Biggadike article demonstrates that it is "demonstrably untrue" that Glaxo used 2'-CDG as a lead compound. (D.I. 150 at 72; DTX 150) At trial, Dr. Schneller noted that in the article, Biggadike and other Glaxo researchers described their synthesis of 2'-CDG. (Tr. 1174:13-1175:20) This article's content had indicated to Dr. Heathcock that, because Glaxo synthesized 2'-CDG and extolled its antiviral activity, this

means that Glaxo was "interested in using it" and had "selected [2'-]CDG as a lead structure to work from." (Tr. 194:3-10) During cross-examination at trial, Dr. Schneller was asked about how the researchers at Glaxo, including Biggadike, had treated 2'-CDG at the time:

Teva's counsel:	And [Biggadike is] one of those people that considered 2'-CDG a lead compound; is that right?
Dr. Schneller:	He –
Teva's counsel:	Back in the eighties, back in the eighties.
Dr. Schneller:	Yes. Biggadike would have been one of those people that could have considered it, yes. I don't know exactly, but I would certainly think he would be one that would have considered it.
Teva's counsel:	Yes. And that's based on articles you've seen that he wrote; is that right?
Dr. Schneller:	Yes, sir.

(Tr. 1167:22-1168:10)

Next, Dr. Schneller was shown the 1988 Borthwick article, which describes how Glaxo researchers made a compound identical to 2'-CDG, except that they attached a fluorine atom to the carbon atom at the 2 prime position. (DTX 170) Dr. Heathcock opined that this article, which explained how this new compound was incredibly potent and active against HSV-1 and HSV-2, showed how Glaxo had in fact used 2'-CDG as a lead compound, with excellent results. (Tr. 197:23-198:3) In its post-trial briefing, BMS argues that the article, which at times also touts the properties of certain acyclic and furanose compounds in treating herpes, would have taught a person of skill in the art *away* from considering a carbocyclic like 2'-CDG a lead compound. (D.I. 150 at 73-74) Yet on cross-examination at trial, after again acknowledging that

he knew that "Glaxo did some modifications of 2'-CDG," (Tr. 1210:21-23), Dr. Schneller was asked about what could be learned from the Borthwick article:

Teva's counsel:	Because we know, we know from this [Borthwick] article, for instance, that people of skill in the art looked at 2'-CDG and made changes to the sugar portion?
Dr. Schneller:	The article says that's what they did, true. . . .
Teva's counsel:	So the folks at Glaxo were making an alteration at the 2' position of the sugar portion of 2'-CDG?
Dr. Schneller:	Yes.
Teva's counsel:	Is that correct?
Dr. Schneller:	Correct. . . .
Teva's counsel:	They are saying they made this change [to the] carbocyclic ring at the 2' position?
Dr. Schneller:	Yes.
Teva's counsel:	And they got more activity?
Dr. Schneller:	They got more activity of their compound compared to, I guess, CDG.
Teva's counsel:	Okay.
Dr. Schneller:	Yeah. I guess that's what it says.

(Tr. 1210:13–23; 1213:19–24; 1215:9-14; 1216:10-18)

Dr. Schneller was also shown the 1989 Montgomery article, which discusses how SRI had identified 2'-CDG as some of the most "promising" and "likely" compounds as to the treatment of herpes infections. (DTX 172) Dr. Heathcock had concluded that the way SRI researchers discussed 2'-CDG in this article was a "lamp post" that "illuminated 2'-CDG as [] a

very exciting lead compound to work from." (Tr. 191:5–10) In its post-trial briefing, BMS asserts that "it is clear that SRI did not use 2'-CDG as a lead compound" and that it only identified the compound as a "potential drug candidate." (D.I. 150 at 72) However, on cross-examination at trial, Dr. Schneller agreed that this article showed that SRI was treating 2'-CDG as a "promising compound." (Tr. 1181:16–20) Whether described as "exciting" (as Dr. Heathcock did) or "promising" (as Dr. Schneller did) the point about 2'-CDG is the same—the 1989 Montgomery article was touting 2'-CDG's promise as a compound with which to work.

Dr. Schneller even confirmed that 2'-CDG had been treated as a lead compound when he examined literature that looked back on this era. On cross-examination, Dr. Schneller was asked about the 1997 Mansour and Storer article, which noted that 2'-CDG had "played a pivotal role in providing a template for the development of carbocyclic nucleoside analog programs." (Tr. 1245:18-22) Dr. Schneller was then asked:

Teva's counsel:	It . . . sounds like [the authors] think this was, 2'-CDG was a lead compound; right?
Dr. Schneller:	That's what they say.

(Tr. 1245:23-1246:1)

Thus, in direct contrast to BMS's arguments in its briefing, the testimony of its own expert at trial repeatedly and conclusively established that researchers were, in fact, treating and using 2'-CDG as a lead compound in the relevant time period. These concessions are not surprising, because in Dr. Schneller's own June 1992 article discussing 2'-CDG, he explained how he and others had prepared "derivatives" of 2'-CDG, and noted that 2'-CDG had shown

significant antiviral activity by that time, citing to the Shealy 1984 article.[26] (DTX 178.0003; Tr. 1189:20-1191:11)

Viewing the prior art as a whole, the Court finds that Teva has clearly and convincingly proved that the chemist of ordinary skill in the art would have selected 2'-CDG as a lead compound as of October 1990.

b. A Person of Ordinary Skill in the Art Would Have a Reason or Motivation to Modify 2'-CDG by Adding a Carbon Atom to Arrive at Entecavir With a Reasonable Expectation of Success.

(1) Reason or Motivation to Modify

Upon a showing by clear and convincing evidence that the skilled chemist would have been motivated to select 2'-CDG as a lead compound, Teva must next prove (clearly and convincingly) that the chemist had "a reason or motivation to modify [2'-CDG] to make" entecavir. *Otsuka*, 678 F.3d at 1292; *see also Takeda*, 492 F.3d at 1357. In line with the flexible nature of the obviousness inquiry highlighted by the Supreme Court in *KSR*, the motivation to select and modify a lead compound need not be found explicitly in prior art references, but may instead come from a number of sources, "including common knowledge, the prior art as a whole, or the nature of the problem itself." *Pfizer*, 480 F.3d at 1362; *see also Matrix Labs.*, 619 F.3d at 1352; *Eisai*, 533 F.3d at 1357. Here, too, "pertinent properties guide the analysis, for 'it is the possession of promising useful properties in a lead compound that motivates a chemist to make

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[26] If there could be any doubt, in light of all of this evidence, as to whether 2'-CDG was treated and used as a lead compound in this time period, it is even further dispelled by the fact that *BMS itself* did so. Although not prior art, and not relied upon by Dr. Heathcock in his analysis, it is worth noting that Dr. Zahler acknowledged that in designing a particular compound at BMS in May 1990, BMS scientists took 2'-CDG, which had activity, substituted an exocyclic methylene at the 2 prime position, and formed a new compound. (Tr. 588:5-10)

structurally similar compounds.'" *Otsuka*, 678 F.3d at 1292–93 (quoting *Matrix Labs.*, 619 F.3d at 1354). The Federal Circuit has emphasized the important purpose of this prong in the obviousness analysis:

> As this court has stated, virtually all inventions are combinations of old elements. Therefore, an . . . accused infringer may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an . . . accused infringer . . . to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention . . . . To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (internal quotation marks and citation omitted).

Teva argues that the ordinary medicinal chemist, having selected 2'-CDG as a lead compound for further development, would have proceeded to make obvious, conservative changes to the structure of 2'-CDG in accordance with the traditional method of drug discovery. (D.I. 151 at 51) Both Dr. Schneller and Dr. Heathcock agreed that when a lead compound is selected, a chemist would seek to make conservative changes to that structure.

The evidence in this case indicates that the prior art would have directed that chemist to look to 2'-CDG's carbocyclic (sugar) portion (rather than the guanine base) to make such changes. This is because, as Dr. Heathcock explained, other chemists were already doing so with positive results, while chemists modifying the guanine base of nucleoside analogs were ending

up with less active compounds. (Tr. 203:6-204:9; JTX 87.0001)[27] At first, on direct examination at trial, Dr. Schneller testified that the person of ordinary skill looking at Shealy 1984 would conclude that "if I am going to use 2'-CDG as a lead compound, I would retain the sugar portion." (Tr. 1134:14–21; *see also* Tr. 1135:7–12) However, Dr. Schneller later acknowledged on cross-examination that other chemists were indeed regularly doing the opposite in the relevant time period; that is, making changes to the sugar portion of 2'-CDG (and finding activity in the resulting compounds). (Tr. 1212:15–1216:18) There appears to have been no reference in any prior art explicitly stating that changes to the guanine base must be avoided, but the prior art did reflect that changes to 2'-CDG's sugar portion yielded compounds with increased activity (and, conversely, that changes to guanine bases of nucleoside analogs resulted in decreased activity). The very goal of structure-activity relationship testing (and thus the goal of the skilled artisan working to develop antiviral drugs) is to create a new compound with improved activity through

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[27] BMS argues that Dr. Heathcock misinterpreted a 1989 article by Michael Harden and Richard Jarvest ("the Harden & Jarvest article"), a prior art reference, in coming to this conclusion. (JTX 87) BMS contends that the article reported that two ganciclovir analogs they had made with modifications to the base showed good *in vitro* activity. (D.I. 150 at 78-79) Therefore, BMS concludes, contrary to Dr. Heathcock's testimony, the article taught the skilled artisan to look to the base to make modifications. (*Id.*) However, no expert for BMS testified about this article. For its part, Teva points out that the article states that the two compounds showing good activity had bases that converted back to guanine, thus leading the authors to speculate that the "formation of the parent guanine" that occurred with these two compounds is what may have caused the activity. (D.I. 157 at 16) In any event, the article clearly begins by stating that "all" analogs of acyclovir synthesized with modifications to their guanine bases by a number of other researchers had "resulted in substantial loss of antiviral potency," which was the substance of Dr. Heathcock's point about the article—that in the main, it summarizes how changes to the base result in less potency than changes to the sugar portion of the compound. (JTX 87.0001; *see also* Tr. 203:6-204:9) The Court is unconvinced by BMS's contention to the contrary.

the process of making small changes to a lead compound. This would have led to a focus on the sugar portion of 2'-CDG.

Once focused on the sugar portion of 2'-CDG, the testimony showed that the skilled artisan would have looked to the most obvious places to make modifications: the 2 prime position and the 5 prime position of the carbocyclic ring. Dr. Heathcock explained this was so because these were open positions where small changes could easily be made, as opposed to the 3 prime position or 4 prime position (the hydroxyl and hydroxymethyl groups), that are positions that "the biochemical machinery is probably recognizing." (Tr. 201:20-202:4) No expert for BMS refuted this contention, and BMS's attempts to do so in its post-trial briefing rely on articles that actually confirm Dr. Heathcock's testimony or post-date the priority date of the '244 Patent.[28]

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[28] BMS contends that several articles contradict Dr. Heathcock's opinion that the ordinary chemist would look to these positions to make modifications, arguing that the prior art shows that the "scientists working in nucleoside analogs actually investigated the 2', 3', 4', 5', and 6' positions." (D.I. 156 at 8; *see also* D.I. 150 at ¶ 42) BMS's citations in support of this argument, however, are not convincing. The Borthwick article encouraged a 2'-*ara*-fluorine substitution over 2'-CDG (adding a fluorine atom at the 2 prime position pointing up), which is exactly what Dr. Heathcock opined was one of the obvious modifications to make. *See supra* ¶¶ 105-06. Shealy 1987 discussed the synthesis of compounds with a hydroxyl group at the 2 prime position instead of the 3 prime position (where the hydroxyl group of 2'-CDG is located), (DTX 125), but none of the analogs in Shealy 1987 were as active as 2'-CDG. (*Compare* DTX 125.0003, tbl.1 (highest VR=3.1 and lowest MIC50=26), *with* DTX 126.0002, tbl.I compound 12 (2'-CDG) (highest VR≥4.6 and lowest MIC50≤0.3)) The Mansour and Storer article noted that an analog with a hydroxyl group at the 4 prime position was the "leading candidate" in the purine series, but this article was published in 1997—several years after entecavir's invention—and it cited to a 1992 article for this proposition, which also post-dates the invention date for the '244 Patent. (DTX 154.0017) The Madhavan group published that they made an analog with an exocyclic methylene group at the 5 prime position and another analog with a fluorine at the 5 prime position, both of which were modifications that Dr. Heathcock opined would be obvious to make as to 2'-CDG. *See supra* ¶¶ 114, 127. Finally, BMS's reference to both the "5'" and "6'" positions is curious, in that both references relate to the same position—that at the top of the five-membered ring—again, a position that Dr. Heathcock opined was a place for obvious

Dr. Heathcock then asserted that in determining what changes to make at the 2 prime and 5 prime positions, the medicinal chemist would be guided, in part, by the periodic table. Dr. Heathcock's use of the periodic table in this regard appears to have led to BMS's critique that he "appeared to draw a motivation to modify 2'-CDG with a[n] exocyclic methylene group from his personal knowledge and general chemistry principles," (D.I. 150 at 77), which purportedly did not reflect what "nucleoside chemists were actually doing in the 1980s," (D.I. 156 at 8).

However, the obvious reality is that the ordinary chemist skilled in the art would be intimately familiar with the periodic table. The Court does not find fault with Dr. Heathcock's consideration of the periodic table in the obviousness analysis. The Supreme Court has held that in determining whether there was "an apparent reason to combine the known elements in the fashion claimed by the patent at issue," courts must keep the analysis flexible and include consideration of, *inter alia*, "the background knowledge possessed by a person having ordinary skill in the art." *KSR*, 550 U.S. at 418. Indeed, if there were any doubt as to the propriety of relying on the periodic table as part of such an analysis, it was quickly dispelled by Dr. Schneller's testimony, in which he agreed with this mode of Dr. Heathcock's analysis:

Teva's counsel:	All right. Now, you would agree that if you are looking for conservative changes that could be made, one place you would look at [is] the periodic table; is that right.
Dr. Schneller:	*Well, you almost have to, because all molecules are made from the elements that are on that periodic table. So there's no magic lamp someplace that's going to come up with new ideas.*

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modifications. (D.I. 156 at 8)

Teva's counsel: And the periodic table . . . it's the chemist's stock in trade?

Dr. Schneller: Yes, sir.

(Tr. 1196:22-1197:9 (emphasis added))

Both experts ultimately agreed that from there, the skilled artisan would focus on the top row of the table, as that contains the smallest elements. Dr. Heathcock pinpointed carbon and fluorine as the two obvious choices. (Tr. 206:8-13) Dr. Schneller agreed, acknowledging that he had previously testified under oath in his deposition that in analyzing which element to choose, he would "rule out everything but the carbon" and that carbon was the "the only one that sticks out." (*See* Tr. 1200:7-14; 1203:1–6; 1206:7-11)[29] These selections equate to a small, finite number of changes to try to the lead compound, 2'-CDG. Specifically, it would leave six options to pursue: binding a fluorine atom up or down at the 2 prime or 5 prime position and binding a double-bonded carbon atom[30] at the 2 prime or 5 prime position (although, as previously noted,

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[29] Earlier at trial, during direct examination, Dr. Schneller had stated that he "disagree[d]" with Dr. Heathcock's selection of carbon and fluorine as the elements the skilled artisan would select in making changes to nucleoside analogs. (Tr. 1116:16–1117:1) Yet on cross-examination, as noted above, he clearly confirmed that carbon would be the medicinal chemist's most conservative change to the five-membered ring—and confirmed that he had said the same thing, repeatedly, during his prior deposition. (Tr. 1199:11–1203:6; 1206:7-13)

[30] While Dr. Schneller did testify that adding a methyl group (a single carbon atom bonded to three hydrogen atoms) would have been a "conservative change" and that the addition of an exocylic methylene group (a carbon-carbon double bond) would have been a "dramatic change," (Tr. 1208:10-1210:12), overall, the testimony conveyed that the skilled artisan would pursue the addition of an exocyclic methylene group at either the 2 prime or 5 prime positions before she would think to add a methyl group. Dr. Heathcock indicated that adding a methyl group would be a second tier (or less conservative) choice because a methyl group is bigger and longer than an exocyclic methylene group. (Tr. 208:12–209:13; 1208:10-1209:24) This is because, as even Dr. Schneller testified, the methylene bond is shorter, which was a "well-known" concept. (Tr. 1206:20–1207:6) In addition, the easiest way to synthesize the carbon-carbon single bond (i.e., methyl) derivative of 2'-CDG would be to make the double bond

Glaxo researchers had already made a compound with a fluorine atom pointing up at the 2 prime position of 2'-CDG).

With regard to whether a particular invention was obvious, the Federal Circuit has noted that "most inventions that are obvious were also obvious to try." *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361 (Fed. Cir. 2011) (quoting *Bayer Schering Pharm. AG v. Barr Labs., Inc.*, 575 F.3d 1371, 1347 (Fed. Cir. 2009)). An invention was "obvious to try" if the skilled artisan has "'a good reason to pursue the known options.'" *Unigene Labs*, 655 F.3d at 1361 (quoting *KSR*, 550 U.S. at 421) However, the Federal Circuit has stressed that in order for an invention to be "obvious to try," the "known options" must have boundaries. *Id.* at 1361. That is, "[e]vidence of obviousness, especially when that evidence is proffered in support of an 'obvious-to-try' theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were 'finite,' 'small,' or 'easily traversed,' and that skilled artisans would have had a reason to select the route that produced the claimed invention." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1072 (citations omitted); *see also OSI Pharm., Inc. v. Mylan Pharm. Inc.*, 858 F. Supp. 2d 341, 358 n.20 (D. Del. 2012).

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compound such as entecavir first, and then do a "very trivial reaction" to entecavir to arrive at Dr. Schneller's methyl substitution. (Tr. 208:15-21; 209:2-6; 1208:10-1209:24) Interestingly, work by BMS employees seems to confirm portions of Dr. Heathcock's analysis here. An internal BMS report covering the period from December 1, 1989 through May 31, 1990 authored by Dr. Tino and Ms. Karen Lis (with a copy to, among others, Dr. Zahler), discloses that the authors had synthesized a guanine analog (compound 14) with an exocyclic methylene substitution at the 2 prime position, which they compared to 2'-CDG (compound 17). (DTX 136.0004) This report cited to the Ueda reference, which disclosed a compound synthesized with an exocyclic methylene substitution at the 2 prime position. (*Id.* at 136.0004, .0009) At trial, Dr. Zahler acknowledged that Dr. Tino's logic in creating compound 14 was that the 2 prime position would be a good place to make a substitution, and that adding an exocyclic methylene group would be a "good kind of substitution to make" (just as Ueda had done to a different lead compound). (Tr. 585:8–587:7) Dr. Tino reported to Dr. Zahler at BMS. (Tr. 574:13–575:5)

The skilled artisan using 2'-CDG as a lead compound in 1990 would have embarked on the "traditional drug" discovery route, the most common and one of only three well known approaches at that time. *See Standard Oil Co.*, 774 F.2d at 454 ("A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate . . . ."); *see also Otsuka*, 678 F.3d at 1296 ("What matters [in considering whether a patent is obvious] is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art."). That chemist would have been motivated to make small, conservative changes to the 2 prime or 5 prime positions of 2'-CDG's sugar portion, in hopes of creating a compound with improved antiviral activity. There were a few prime options for the skilled artisan to pursue in that regard, as laid out above, and BMS's own expert has confirmed that the most conservative of those—the one that "sticks out"—would have involved the addition of a carbon. Courts have indicated that a change like this, supported by sufficient motivation, can bolster a patent challenger's argument on this prong of the analysis. *See, e.g.*, *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, Civil Action No. 3:07-cv-01000 (MLC), 2010 WL 4596324, at *21 (D.N.J. Nov. 15, 2010) ("We accept Defendants' contention that a skilled artisan would have been motivated to experiment with a lead compound by varying the length of the linker . . . because 'homologation' is the simplest change a medicinal chemist can make to a compound in terms of evaluating structure-activity relationships.").[31] One

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[31] *Cf. Takeda*, 492 F.3d at 1360 (affirming district court's holding that a patent was valid in part because the "district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds," because, contrary to defendant's expert's testimony, the court found that the defendant's proposed steps did not constitute a routine process of modifying lead compounds at the time of the invention).

of those few changes, substituting a double carbon atom at 2'-CDG's 5 prime position, is the substitution that creates entecavir.

Moreover, in the relevant time frame, other chemists were (1) making changes to carbocyclic nucleoside analogs by adding an exocyclic methylene group to the sugar portion; (2) making such changes to 2'-CDG; and (3) making such changes to the 5 prime position of a carbocyclic's five-membered ring. As an initial matter, Dr. Schneller agreed that exocyclic methylene groups were "not a new concept in the 1980s" in the context of "nucleoside analogs." (Tr. 1218:8–1226:17) In 1988, the Takenuki article disclosed carbocyclic nucleoside analogs that had been made with exocyclic methylene groups substituted at the 2 prime position. (JTX 83; Tr. 216:12-217:1) In 1989, the Ueda article also disclosed carbocyclics that were made with exocyclic methylene groups at the same position, some of which "exhibited potent activity" against the herpes viruses. (JTX 88.0010; Tr. 217:6-219:4)

Additionally, inspired by Ueda, late in 1989 or in early 1990, chemists *from BMS itself*, including Dr. Tino and Ms. Karen Lis, made at least one guanine analog with an exocyclic methylene group at the 2 prime position *using 2'-CDG as a lead compound*:

Teva's counsel:	And so what [Dr. Tino] did was, he said . . . [w]e'll take 2'-CDG, which is active, and try that exocyclic methylene at the 2' position for 2'-CDG; is that right?
Dr. Zahler:	That was probably his logic. I concur with that, yes. Fine.

(Tr. 588:5–10) This BMS-created compound, referred to in the internal report as compound 14, had a guanine base. (Tr. 583:13–17; DTX 136) The article cites the 1989 Ueda article as part of

its inspiration for adding an exocyclic methylene group to the sugar portion of 2'-CDG. (DTX 136.0004, .0009)

In 1988, another group of chemists led by Madhavan made a carbocyclic analog using aristeromycin as a lead compound. Madhavan substituted an exocyclic methylene group at the 5 prime position of the lead—the same position as the addition of the exocyclic methylene group in entecavir—creating the compound known as Madhavan 30, which was discussed in a 1988 article. (Tr. 212:8-216:9) Madhavan 30 was found to be the most potent of the compounds synthesized by the group, which also included analogs containing a fluoro substitution at the 5 prime position (another of the obvious substitutions that Dr. Heathcock noted one might consider making to 2'-CDG). (Tr. 212:5-214:7) Dr. Zahler was aware of the Madhavan article when he invented entecavir, and in fact it was cited as the most relevant piece of prior art in the '244 Patent application.

Because Madhavan had utilized an exocyclic methylene group at the same position (the 5 prime position) where that group is found in entecavir, testimony at trial regarding whether a person of skill in the art in the relevant time frame would have been motivated by Madhavan (and these other references) to make a similar substitution to 2'-CDG was particularly important. For his part, Dr. Heathcock testified clearly that in light of the Madhavan reference (and the other references listed above), a person of skill in the art would have had reason to make such a substitution. (Tr. 219:5-9; 221:13-14; 228:11-17)

In response to this testimony, BMS argues that "*as Dr. Schneller testified*, the fundamental differences between 2'-CDG and the molecules in the Madhavan article would have discouraged any combination of the molecules from the two articles." (D.I. 150 at 79) (emphasis

added) BMS continues that this is so because "[t]he molecules had different viral targets (with Madhavan indicating that his compounds lacked substantial anti-herpes activity), different enzymatic targets, different mechanisms of action, and different preserved structures" and because both molecules were toxic. (*Id.*) It is true that on direct examination at trial, Dr. Schneller repeatedly testified, without equivocation, that not only would a person of skill in the art be "discouraged" from making this modification to 2'-CDG, but that it would have been "out of the question" for one to think to do so. (Tr. 1123:21–1124:2; 1125:2–5; 1126:10–15; 1130:14–21; 1131:23–1132:3; 1136:11–16)

Yet just minutes later, on cross-examination, Dr. Schneller was forced to acknowledge that such statements were in conflict with what he had previously written in his expert report, and what he had testified to in his prior deposition. In Dr. Schneller's expert report, when addressing the Madhavan group's results, he had stated, *inter alia*, that "[t]his mechanism of antiviral activity through toxicity to the host would certainly not suggest that one of ordinary skill in the art should make an antiviral molecule with a 6' exocyclic methylene group, *but it might not dissuade a person of ordinary skill in the art from making a molecule with a 6' exocyclic methylene group.*" (DTX 239.0029; Tr. 1228:13–1229:8 (emphasis added)) Then, Dr. Schneller stated that in his expert report, when he noted that a chemist would not be dissuaded from making this change after reading Madhavan, this "would mean [Madhavan] *would persuade*" a chemist to do so. (Tr. 1229:9-15) (emphasis added) Dr. Schneller had to acknowledge the reality that, at a minimum, the meaning of the statements he made in his expert report on this crucial point were far different than what he had testified to on direct examination—when he had asserted that the skilled artisan would affirmatively be *discouraged* from making the

modification, or that such actions would be "out of the question" for that chemist. (Tr. 1229:24-1230:3) He admitted that when he filled out his expert report, he had meant to give an honest rendition of his opinions, and was careful in the language that he had selected to do so. (Tr. 1230:4-11)

Then, Dr. Schneller was asked additional questions about what his testimony had been on this topic at his prior deposition. This exchange was as follows:

Teva's counsel:	All right. And, sir, you actually said under oath in your deposition that the Madhavan article *could have led* a person of skill in the art to seek drug discovery targets guided by combining the features reported in Madhavan with those in Shealy. You said that in your deposition, didn't you.
Dr. Schneller:	Yes, sir.
Teva's counsel:	That's very different from saying that Madhavan would discourage somebody from making that substitution.
Dr. Schneller:	Yes, sir.
Teva's counsel:	So, sir, when you testified under oath and you wrote your expert report and you signed it, you were giving us truthful, honest testimony about your opinions; is that right?
Dr. Schneller:	Of course.
Teva's counsel:	And we can count on those; is that right?
Dr. Schneller:	Yes, sir.
Teva's counsel:	We can rely on those as your true opinions in this case?
Dr. Schneller:	Yes, sir.

(Tr. 1231:18–1232:17) (emphasis added)

In sum, just as Dr. Heathcock testified that a skilled artisan would have been motivated to make this modification, BMS's own expert, Dr. Schneller, has also acknowledged that this artisan could well have been led to do so.[32] The Court has considered these portions of the trial testimony carefully, and finds that the powerful admissions by BMS's expert severely undercut BMS's arguments to the contrary regarding motivation to combine.

There are additional flaws in those arguments. While BMS attempts to argue that Madhavan 30's toxicity would discourage the skilled artisan from using it as the basis for a drug, (D.I. 150 at 79-80), the asserted lead compound here is 2'-CDG, not Madhavan 30. As already explained, 2'-CDG's toxicity was not clearly known to researchers during the relevant time period and had not discouraged them from using 2'-CDG as a lead compound. In any event, Madhavan 30's toxicity data would not "put off" a medicinal chemist from making similar substitutions, because while it shows that the basic lead compound itself, aristeromycin, was "pretty cytotoxic," it was not clear whether that toxicity was triggered by the exocyclic methylene group itself or "due to the overall structure of [] the series they're working in." (Tr. 214:24–215:9) Moreover, as Dr. Heathcock testified, it is not necessarily only the Madhavan article itself that would inspire the skilled artisan working with 2'-CDG to add an exocyclic methylene group to the 5' position of 2'-CDG. Rather, Dr. Heathcock explained that his opinion was that:

> [I]t would have been obvious to change [2'-]CDG by adding [a] methylene group. Not that [the person of ordinary skill in the art would have]

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[32] On redirect examination at trial, Dr. Schneller was asked four questions, none of them about these portions of his testimony. (Tr. 1250:7-1251:17)

> decided to add a methylene group because Madhavan had, but [Madhavan shows] other medicinal chemists working on antivirals, admittedly with an idea that they're going after a different enzyme. But they wanted to also change their lead compound in a small way, and they used this same change [to their lead compound]. . . . What the Madhavan paper does is simply support my opinion. It shows that someone else thought of doing it and they did it.

(Tr. 311:15–24; 313:1-4)[33] As explained above, others were also making this change, albeit to the 2' position of the carbocyclic ring of various nucleoside analogs (including, in fact, BMS itself as to 2'-CDG). Many of the resulting compounds exhibited antiviral activity, thus teaching the medicinal chemist of ordinary skill that such a substitution would yield a compound with similar activity. Accordingly, then, as Teva argues, "[t]he ordinary chemist would do the same to 2'-CDG."[34] (D.I. 157 at 34)

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[33] The Court understands the combined effect of Dr. Heathcock's testimony to be that (1) the ordinary chemist would have been aware of the Madhavan article and would have treated it as motivation to make the same substitution to 2'-CDG; and (2) even had that chemist not seen the reference, its existence corroborates Dr. Heathcock's testimony that such a chemist would think to make this kind of change. (*See also* Tr. 215:14-24; 228:11-17; 310:1-4)

[34] *Compare Novartis Pharm. Corp.*, 2007 WL 2669338, at *8 (rejecting plaintiff's argument that it was non-obvious to modify the lead compound since there were "'numerous possible substitutions' that could have been made at the 2 position and 6 position," because "the 6-deoxy modification had proven to be several times more effective than any other substitutions" and therefore "the 6-deoxy would have been one of the first options explored by one skilled in the art"), *with Eli Lilly and Co. v. Zenith Goldline Pharm., Inc.*, 364 F. Supp. 2d 820, 904–05 (S.D. Ind. 2005) (rejecting defendant's argument that the skilled artisan would have been motivated to modify flumezapine by replacing its fluorine atom with a hydrogen atom, because the "prior art taught that . . . replacing the fluorine atom with a hydrogen atom in a structurally similar compound would produce a compound having less activity than clozapine, the benchmark compound" and "[i]n view of the necessity of maintaining activity, replacing the fluorine atom with a hydrogen atom would not have been the obvious choice").

As to BMS's argument that one would avoid combining Madhavan 30 with 2'-CDG because the compounds had different enzymatic targets, Dr. Schneller testified at his deposition that the skilled chemist would have had *no reason to believe* that adding a methylene at the 5 prime (or 6 prime) position would inhibit the binding of the molecule to the enzyme active site—testimony that he confirmed on cross-examination. (Tr. 1231:5-13) He admitted that his deposition testimony and his direct testimony at trial were different in that regard. (Tr. 1231:14-17 ("Q: That's different from saying that Madhavan would discourage somebody? A: That's different than saying it. Yes.")) And finally, considering BMS's argument that one would not combine features of the two compounds because they have different mechanisms of action, on cross-examination, Dr. Schneller acknowledged that an ordinary medicinal chemist undertaking the traditional approach to drug discovery typically *does not know* anything about "the mechanism of action of the [compounds] involved." (Tr. 1150:4–14) As before, in these key areas, Dr. Schneller's testimony on cross-examination is divergent to BMS's post-trial arguments.

Taking all of the above factors into account, the Court finds that Teva has proved by clear and convincing evidence that an ordinary medicinal chemist, having selected 2'-CDG as a lead compound, would have had reason to and been motivated to substitute an exocyclic methylene group at the 5 prime position "because there were other compounds like that that had already been made" and that chemist would expect the analog to "have similar biological properties to [2'-]CDG itself, which were good properties." (Tr. 219:5–18) As Dr. Heathcock testified, in light of the prior art and the background knowledge of the skilled artisan, "the substitution of a

methylene group to [2']-CDG to arrive at entecavir" was an "obvious modification." (Tr. 221:8–14)

(2) Reasonable Expectation of Success

As indicated above, it is not enough for a patent challenger to prove that the prior art would have supplied the skilled artisan with a reason or motivation to modify a lead compound to make the claimed invention. Teva must also prove that the chemist of ordinary skill would have been motivated to make the claimed compound "with a reasonable expectation of success." *Otsuka*, 678 F.3d at 1292; *Pfizer*, 480 F.3d at 1361. The Federal Circuit has stressed that "[c]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364.

In cases involving the chemical arts, "'it is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation in light of the totality of the prior art, that the new compound will have similar properties to the old.'" *Otsuka*, 678 F.3d at 1293 (quoting *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007)); *see also Eisai*, 533 F.3d at 1357. The skilled artisan's reasonable expectation of success is measured "as of the date of the invention[]." *Amgen Inc.*, 580 F.3d at 1362 & n.9.

Here, as explained above, 2'-CDG and entecavir were structurally very similar. *See supra* Section I.B.1.a.(2)(a). It is well-settled that structurally similar compounds "often have similar properties." *Takeda*, 492 F.3d at 1356 (quoting *In re Deuel*, 51 F.3d at 1558); *see also Altana*, 566 F.3d at 1007; *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) ("the presumption [is] that

similar compositions have similar properties"). Based on the structural similarity between the two compounds, Dr. Heathcock opined that the skilled artisan, upon modifying 2'-CDG with an exocyclic methylene group at the 5 prime position, would have expected entecavir to have "similar biological properties to CDG itself." (Tr. 219:5–18; *see also* 229:14–19) Indeed, this assumption is reflected in the hypothesis known as SAR, which is the "the basic tenet by which medicinal chemists operate." (Tr. 145:2-14 ("[I]f you have two compounds that are similar in structure, they will have similar activity."); *see also* DTX 170 (1988 Borthwick article describing how attaching flourine atom to the carbon atom at the 2 prime position of 2'-CDG created new compound with similar, even enhanced, antiviral properties against HSV-1 and HSV-2))

There is other corroborating evidence that confirms the Court's conclusion that a person of skill in the art could have reasonably expected the substitution of a exocyclic methylene group at the 5 prime position of 2'-CDG to create a compound that had similar properties to 2'-CDG, including antiherpetic activity. For example, in the relevant time period, BMS itself had designed an analog of 2'-CDG with an exocyclic methylene substitution to the 2 prime position, and accurately predicted (citing, in part, to the Shealy '255 Patent) that the analog would have similar activity to 2'-CDG, based on the modeling of their respectively similar three-dimensional conformations.[35] (Tr. 596:6-14; DTX 136.0004; DTX 141.0001-.0002, 0005-.0008)

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[35] Similarly, at the time of entecavir's creation, BMS's use of three-dimensional computer modeling confirmed that it expected entecavir and 2'-CDG to have similar activity. BMS's modeling results found that both entecavir and 2'-CDG fell within a "region of conformation natural space that could predict bioactivity or could be used to predict bioactivity." (Tr. 565:8-566:4; 656:21-660:24) Although, as previously noted above, a person of ordinary skill in the art would not typically be thinking of these compounds in three dimensions, this only serves to further underscore the likelihood of similar bioactivity between entecavir and 2'-CDG at this time.

In addition, the analogs with exocyclic methylene groups synthesized by the Madhavan group, albeit using different lead compounds, demonstrated that such substitutions resulted in compounds that retained the antiviral activity of the lead compound. (Tr. 227:1–6) For instance, as to the compounds aristeromycin and Madhavan 30 (where the only difference between the two is the presence of an exocyclic methylene substitution at the 5 prime position), those compounds showed similar activity. (Tr. 227:1-228:10; 1237:8-1238:23; DDX 63) Dr. Heathcock noted that the creation of Madhavan 30 was "a case where they made this kind of change[,] [i.e., exocyclic methylene substitution,] on a lead compound, and they got compounds with similar activity." (Tr. 228:8-10) Dr. Schneller had "no dispute" with Dr. Heathcock's analysis as to that point. (Tr. 1237:8-1239:21) Dr. Heathcock then concluded that Madhavan's results would be precedent to suggest that "if you made a similar change on 2'-CDG . . . you should also expect to get similar biological activity." (Tr. 228:11-17)

Similarly, the 1989 Ueda article disclosed that an antiviral carbocyclic nucleoside with an exocyclic methylene group "retains a similar overall conformation" to that of the parent natural nucleoside (i.e., the compound *lacking* the exocyclic methylene group). (JTX 88.0010; DDX 103 (Ueda #16); Tr. 217:24-218:19; 1224:1-5) That is, "[e]ven though the double bond had been added, it didn't change the three-dimensional shape of the molecule significantly." (Tr. 218:16-18)

As Teva argues, 2'-CDG showed good antiviral activity at the time of the invention (and its toxicity was not yet well known), just as analogs made with exocyclic methylene substitutions

did. Therefore, the skilled artisan would have reasonably expected entecavir to have similarly strong antiviral activity as did 2'-CDG.[36] (D.I. 151 at 56; D.I. 157 at 37)

Moreover, the skilled artisan would have expected to be able to synthesize entecavir, using 2'-CDG as a lead compound. Dr. Heathcock testified that, given that "synthetic organic chemistry" is the "stock and trade" of a medicinal chemist, and because the "tools that you need to make entecavir were all out there in the literature," an ordinary medicinal chemist would have been able to synthesize entecavir after having conceived of it. (Tr. 221:18-222:12) Dr. Slusarchyk's testimony supports this point, as when Dr. Zahler went to him with the idea for entecavir, Dr. Slusarchyk immediately had a "very good idea" of how to make the compound, (Tr. 503:10-14), and said that, although it would be challenging, he "expected to be able to [synthesize entecavir] with [his] skills as a chemist," (Tr. 506:23-507:5). Dr. Slusarchyk

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[36] BMS's arguments regarding reasonable expectation of success do not persuade the Court otherwise. Notably, BMS's opening brief fails to address this factor of the *prima facie* case in any great detail, simply asserting that "there would be no expectation of success due to 2'-CDG's extreme toxicity." (D.I. 150 at ¶ 140; *see also id.* at 102 ("[A]ny examiner would have understood that 2'-CDG was "highly toxic" and would not have served as an appropriate basis for modification with a reasonable expectation of success.")) However, as previously discussed, 2'-CDG's toxicity was not well known at the time of the invention and therefore would not have impacted a reasonable expectation of excess. In its responsive brief, BMS contends that "[t]he prior art actually suggests that one could not predict that entecavir would have any antiviral activity, and it would have been especially unreasonable to expect antiherpetic activity." (D.I. 156 at 11) At least one reference that BMS cites, in support of the proposition that other similar substitutions had shown no biological activity, is an internal BMS document and is thus not prior art, (DTX 141.0005). And while another reference, the Ueda 1989 article, called out compound 16 for its anticancer activity, it reported that another analog with the exocyclic methylene at the 2' position (2'-methylidenethymidine) "exhibited potent activity for HSV-1," a point confirmed by Dr. Schneller during cross examination. (Tr. 1221:16–1222:15; 1225:5–1226:13) As for the rest of the cited references, no expert for BMS testified about them in this context. In the absence of such testimony, the fact that some such substitutions may not have generated similar activity in the past does not meaningfully impact the Court's conclusion as to the *reasonable* expectation of success that might have been expected here.

synthesized entecavir based in part on his "review of the literature," including the Biggadike reference, explaining that he knew how to perform this synthesis because there were "tons of references" available. (Tr. 503:21-506:2) He noted that "like a good chemist should do" he simply needed to "just put the pieces together," (Tr. 506:17-18), and that this process was something that was "generally known by chemists," (Tr. 506:3-11).

Accordingly, as of October 1990, the evidence clearly and convincingly demonstrates that entecavir and 2'-CDG possessed a sufficiently close relationship to create a reasonable expectation in light of the totality of the prior art, that entecavir would have had similar properties to 2'-CDG. *See Otsuka*, 678 F.3d at 1293. The evidence also suggests that the chemist attempting to do so would reasonably expect to be successful in synthesizing the new compound. Therefore, the Court finds that Teva has met its burden as to this last portion of its *prima facie* case.

2. Objective Considerations of Nonobviousness

With Teva having met its burden to establish a *prima facie* case of obviousness, the Court will go on to consider the fourth *Graham* factor: facts regarding objective indicia of nonobviousness. It is well-settled that "all evidence relevant to obviousness or nonobviousness be considered, and be considered collectively." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1078.[37] As they can give "light to the circumstances surrounding the origin of the subject matter sought to be patented," *Graham*, 383 U.S. at 17–18, objective considerations serve as a check against hindsight bias and "'may often be the most probative and cogent evidence in the

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[37] In other words, the "fact finder[] must withhold judgment on an obviousness challenge until it considers all relevant evidence, including that relating to the objective considerations." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1079.

record.'" *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1075-76, 1079 (quoting *Stratoflex, Inc. v. Aeroquip Corp*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983)). Indeed, these considerations can have the force of "'establish[ing] that an invention appearing to have been obvious in light of the prior art was not.'" *Id.* at 1075–76 (quoting *Stratoflex*, 713 F.3d at 1538–39). As BMS notes in its briefing, (D.I. 150 at 64 n.4), these are not "after-the-fact considerations," nor should they be relegated to "secondary status," but instead should be considered together along with all of the other evidence on obviousness or nonobviousness. *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1078 (internal quotation marks and citations omitted). The Court will now consider each of the objective considerations raised by the parties.

a. Copying

Generally, "[c]opying is an indicium of nonobviousness, and is to be given proper weight." *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 679 (Fed. Cir. 1988). BMS notes that Teva has chosen to copy entecavir, when it had other options, as there "are several other FDA-approved hepatitis B drugs" on the market to choose from. (D.I. 150 at 91; D.I. 156 at 20) It argues that this choice should be regarded by the Court as establishing a secondary consideration of nonobviousness in its favor. (D.I. 150 at 91; D.I. 156 at 20)

While some cases have declared that copying can be a forceful secondary consideration of nonobviousness in ANDA cases,[38] in cases such as *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329 (D. Del. 2009), this Court has concluded that in the

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[38] In support of its argument, BMS cites to one such district court case from 2004. (D.I. 156 at 20 (citing *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 759 (N.D. W. Va. 2004) ("Thus, the Court finds that Mylan's decision to copy LEVAQUIN instead of FLOXIN is significant evidence of non-obviousness, particularly in light of Mylan's lack of success in marketing its own respiratory quinolone.")).

Hatch-Waxman context, "a showing of copying . . . is not compelling evidence [of nonobviousness]." *Id.* at 373; *see also Allergan, Inc. v. Watson Labs., Inc.-Florida*, 869 F. Supp. 2d 456, 485 (D. Del. 2012); *Aventis Pharma S.A. v. Hospira, Inc.*, 743 F. Supp. 2d 305, 349 (D. Del. 2010). In affirming the *Purdue Pharma* decision, the Federal Circuit agreed with this Court's analysis, noting that "we do not find compelling Purdue's evidence of copying in the ANDA context where a showing of bioequivalency is required for FDA approval." *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 F. App'x. 978, 983 (Fed. Cir. 2010); *see also Novo Nordisk A/S v. Caraco Pharm. Labs.*, 775 F. Supp. 2d 985, 1017 (E.D. Mich. 2011) (citing the Federal Circuit's decision in *Purdue Pharma* and following its rationale). Although BMS suggests that copying should be given more weight here since there were a number of other FDA-approved drugs to treat hepatitis B that Teva could have copied, (D.I. 150 at 91; D.I. 156 at 20), at least one district court, citing the Federal Circuit's decision in *Purdue Pharma*, has rejected copying as a compelling consideration in an ANDA case, even where the defendant could have chosen to copy another drug in the relevant market. *See Mitsubishi Chem. Corp. v. Barr Labs., Inc.*, 718 F. Supp. 2d 382, 443-44 (S.D.N.Y. 2010) (rejecting the argument that defendants' copying of the claimed invention, where another available formulation could have been copied, is a factor in the obviousness calculus, because the "burdensome NDA procedures provides generic drug manufacturers with an incentive to copy an already approved drug, so that they can avail themselves of the less burdensome ANDA procedures of the Hatch-Waxman Act").

Teva admits that it has chosen to copy entecavir. However, in light of the incentive provided by the Hatch-Waxman Act for a company like Teva to copy entecavir, the force of that bare choice is diminished, as compared to what it might suggest in an industry without such a

regulatory scheme.[39] Nor is there much (if any) evidence in the record regarding how or why Teva made the choice (as opposed to choosing to copy other options, like tenofovir), and BMS cites to no such evidence in the portions of its post-trial briefs that address the copying issue. (D.I. 150 at 91; D.I. 156 at 20) The Court, following the direction of the Federal Circuit and this Court's case law, finds that Teva's choice to copy entecavir, while not irrelevant to the obviousness analysis, does not amount to compelling evidence of nonobviousness here.

b. Commercial Success

The secondary consideration of 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 Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). "Thus, the law deems evidence of (1) commercial success, and (2) some causal relation or 'nexus' between an invention and commercial success of a product embodying that invention, probative of whether an invention was non-obvious." *Id.*

BMS contends that Baraclude is commercially successful, a fact demonstrated by its substantial sales and market share performance. (D.I. 150 at 84–85; D.I. 156 at 18–19) Further,

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[39] Nor has BMS put forward any additional evidence of copying, beyond Teva's ANDA filings. *See, e.g., Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 876 F. Supp. 2d 295, 419 (S.D.N.Y. 2012) (finding that defendants' "deliberate copying of the inventions provides additional evidence of non-obviousness" in ANDA case, where there was also evidence that defendants had tried to develop alternative processes to manufacture the copolymer at issue, before settling on the claimed methods); *Otsuka*, 2010 WL 4596324, at *26 (noting that evidence of copying has generally been recognized as weak in ANDA cases, but finding that evidence had more force because plaintiff had "introduced evidence of copying beyond Defendants' ANDA filings").

BMS posits that there is a nexus between the drug's commercial success and entecavir, the invention claimed by the '244 Patent. (D.I. 150 at 85–86)

As to BMS's arguments, in terms of raw sales revenue figures, Baraclude has been commercially successful. The Federal Circuit has noted that commercial success "'is usually shown by significant sales in a relevant market.'" *Ecolochem, Inc.*, 227 F.3d at 1377 (quoting *J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997)); *see also Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. USA, Inc.*, Civil Action No. 07-CV-5855 (DMC), 2010 WL 2428561, at *15 (D.N.J. June 9, 2010). BMS has earned $3.8 billion from worldwide sales of Baraclude from its launch in 2005 through 2011, and has seen increasing unit sales of the drug, period over period, since its launch. *See supra* ¶¶ 144-45. In the United States alone, Baraclude has generated $835 million of total revenue during this period. *See supra* ¶ 145. These are clearly not small numbers. *See Alcon, Inc. v. Teva Pharm. USA, Inc.*, 664 F. Supp. 2d 443, 464 (D. Del. 2009) (noting that drug-at-issue had been a "commercial success" by citing to fact that it has "resulted in hundreds of millions of sales"). Indeed, as one court put it, "[s]trong evidence of commercial success is not surprising in a case under the Hatch-Waxman Act" because if the patented drug were not a commercial success, at least to some degree, "generic manufacturers would have little interest in offering their own versions of the drug." *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, No. IP 99-38-C H/K, 2001 WL 1397304, at *12 (S.D. Ind. Oct. 29, 2001). In that regard, Baraclude's annual sales well exceed the approximately $30 million per year sales target (as to drugs with flat or growing revenue) that Teva analyzes in determining whether to develop a generic drug. (Tr. 1265:8-1266:5)

Teva argues that these sales figures might stem from something other than the claimed invention (such as price or promotion activities), pointing only to a fairly general statement from BMS's former Senior Product manager that "nonclinical attributes" might "driv[e] customers" in this market. (D.I. 151 at 66; Tr. 1263:5–10) However, Baraclude was priced at a premium over its competitors, and thus it is hard to argue that a low-pricing strategy drove Baraclude's sales. *See supra* ¶ 152. Moreover, BMS's expert, Mr. Tate, testified that the drug's sales do not appear to be directly tied to marketing, because BMS has spent less money on marketing, advertising, and promoting Baraclude each year while its revenues from the drug have steadily climbed, and because BMS's sales force is similar in size to that of its nearest competitors. *See supra* ¶¶ 153-54.[40] Accordingly, BMS has sufficiently demonstrated a nexus between Baraclude's commercial success and entecavir, the invention covered by claim 8 of the '244 Patent.

However, Teva rightly notes that in addition to bare sales figures, it is important to also look to whether the sales of the product at issue "represent a substantial quantity in the market" *In re Applied Materials, Inc.*, 692 F.3d 1289, 1300 (Fed. Cir. 2012) (internal quotation marks omitted), since the use of sales figures "without any evidence giving context to such figures" is not "compelling," *Purdue Pharma*, 377 F. App'x at 983. Here, the record is a bit more nuanced.

On the one hand, Baraclude's launch caused a steady, continuing decline in the market share of the leader at the time, Hepsera (the brand name for adefovir). *See supra* ¶ 147. By early 2009, Baraclude had established itself as the number one hepatitis B drug on the market,

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[40] There is less evidence in the record as to how BMS's revenue spent on marketing compares to the amounts spent by its competitors, though Mr. Tate did testify that he was able to obtain certain information that suggested the amounts were similar in nature for Baraclude and its current lead competitor, Viread. (Tr. 1295:15-1296:20)

reaching a peak market share of 36 percent. *See id.* And although its percentage of the market had dropped to 34 percent at the time of trial, Baraclude still shares the market lead with Viread (the brand name of tenofovir, Baraclude's now-primary competitor). *See supra* ¶¶ 147, 151.

Yet Baraclude was somewhat slow to take hold in the market for hepatitis B drugs; a year after it debuted (April 2006), it trailed the market leaders Hepsera (which held 55% of the market) and Epivir (the brand name for lamivudine, which held 29% of the market) by a significant margin (as it occupied only 16% of the market). *See supra* ¶¶ 147-48. Three years after going to market, Baraclude still trailed Hepsera (which held 42% of the market to Baraclude's 33%), and did not catch up to Hepsera in terms of market share until October 2008. *See supra* ¶ 148. BMS viewed this performance as "sub optimal," as Baraclude had failed to meet its own internal expectations for market share and sales performance. (Tr. 1261:16-1262:2)*; see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1357 (Fed. Cir. 2012) (noting that product's failure to meet company's own internal projections was relevant to commercial success analysis). That performance also paled in comparison to the initial performance of other hepatitis B drugs released in the 2000s, such as that of Hepsera (which, one year after launch, had 41% of the market) and Viread (which, one year after launch, had 26% of the market in a crowded field of five competitors). *See supra* ¶ 150.

Indeed, for all of the years that Baraclude has been available on the market, over half of the prescriptions written for hepatitis B treatments have been (and continue to be) written for some other hepatitis B drug. By May 2010, BMS was forced to send its sales employees an urgent memo instructing them to stop claiming that Baraclude was the number one drug in the

market, because Viread had caught up to Baraclude in terms of market share, after Viread had been on the market for less than two years. (JTX 37)

In the end, Baraclude's sales performance has shown steady, significant growth, and though it has fought for market share with a crowded field of competitors (including Viread, which has had a more dynamic entry into the market), its share of the market has been significant for most of the years since its launch. "There is no requirement that the invention be the only successful product in its market niche or the most successful." *Takeda Chem. Indus., Ltd. v. Mylan Labs. Inc.*, 417 F. Supp. 2d 341, 386 (S.D.N.Y. 2006). The Court concludes that Baraclude has been a commercial success, though a less dynamic one than BMS asserts in its briefs.

c. Skepticism

"General skepticism of those in the art . . . is also 'relevant and persuasive' evidence of nonobviousness." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 885 (Fed. Cir. 1998) (internal quotations and citation omitted). This is so because "[p]roceeding contrary to the accepted wisdom is . . . strong evidence of unobviousness." *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 668 (Fed. Cir. 2000) (internal quotation marks and citation omitted). BMS hinges its skepticism argument solely on the live testimony of its expert, Dr. Gish, who stated that he and "most of the people in [his] community" were skeptical in 2001 and 2002, when entecavir was being developed and taken to full clinical trials, that a single drug such as entecavir could control hepatitis B in their patients.[41] (Tr. 1352:15-20; *see* D.I. 150 at 90; D.I. 156 at 17)

[41] BMS focuses its skepticism argument on the 2001-2002 time frame, apparently because the sole evidence of skepticism it puts forward is the testimony of Dr. Gish, who "first learned" about entecavir at this time. (Tr. 1352:10-20) This time frame is over a decade after

Dr. Gish's testimony alone here fails to persuade the Court that there was general skepticism towards entecavir in the medical community in this time period, amongst treaters of hepatitis B. At the outset, it is notable that Dr. Gish did *not* testify that he and others were skeptical that entecavir would not be effective in treating hepatitis B at this time; rather, the skepticism was apparently that entecavir would not work as a single form of treatment. (Tr. 1352:2-1353:20)

Moreover, Dr. Gish stated that he expressed his skepticism about entecavir to other physicians in "[m]any different meetings" and to BMS, even calling a meeting with BMS for the purpose of reviewing all of the literature available on the compound. (Tr. 1353:21-1355:23) This meeting, which Dr. Gish attended with other advisors and BMS employees, resulted in the conclusion that "the benefit [of entecavir] was going to far outweigh any risk," prompting the advisors to go from "skeptical . . . to more enthusiastic" and to give BMS the "green light" to proceed through Phase 2/3 trial development for licensing. (Tr. 1355:14-23) The substance of this testimony—that when Dr. Gish actually examined the existing data regarding entecavir's test results at the meeting, he became enthusiastic and gave the project the "green light"—is not all that different from the testimony of Teva's expert, Dr. Thio. Dr. Thio noted her opinion that, in this time frame, "there was no reason to be skeptical that [entecavir] would [not] work well in

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entecavir was invented. The Court notes case law from the Federal Circuit and this Court that tends to peg the relevant time period for analyzing skepticism earlier, in cases noting that "skepticism of skilled artisans *before the invention*" can help to show that the invention was not obvious. *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998) (emphasis added); *Allergan*, 869 F. Supp. 2d at 484; *Aventis Pharma S.A.*, 743 F. Supp. 2d at 344. In its briefing, BMS did not cite to any evidence regarding skepticism involving entecavir in that earlier time frame. Nevertheless, the Court will analyze the impact of the proffered evidence of skepticism that *was* put forward, though ultimately concluding that it does not contribute to a conclusion of nonobviousness.

humans" in that "with all the in vitro data, if anything, people should have been optimistic about it and say [that entecavir was] probably going to work well on humans." (Tr. 466:12-467:7)

The sum total of the evidence regarding skepticism was also particularly thin. BMS offered no documents or exhibits expressing initial skepticism about entecavir in this time frame. Dr. Gish's testimony is the sole proffered basis for such skepticism, and that testimony was not particularly specific (as, for example, Dr. Gish did not provide any details about the meetings at which he expressed such skepticism, or about others with whom he spoke who supported that view). *See Allergan*, 869 F. Supp. 2d at 490 (rejecting plaintiffs' skepticism argument because, *inter alia*, "no written or published statements of skepticism . . . were introduced into evidence to support [another pharmaceutical company's] alleged rationale" and some of the testimony related to "out-of-court statements" of "unnamed" employees); *see also Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 457 (D. Del. 2010), *aff'd in relevant part by* 694 F.3d 1344 (Fed. Cir. 2012).

This lack of detail matters. For example, Dr. Gish testified that prior experience with lamivudine and adefovir, two hepatitis B drugs that had eventually developed resistance problems after promising starts, contributed to his skepticism that no "single drug" would help hepatitis B patients alone. (Tr. 1353:2-9) But Dr. Thio drew a different conclusion that is equally plausible, opining that in light of tenofovir's reported success with co-infected patients at this time, entecavir's positive test results would have made researchers quite optimistic about entecavir's potential. (Tr. 466:10-468:10) In the absence of additional corroborating evidence to support Dr. Gish's differing view, his verbal claim of skepticism is simply not enough to weigh in BMS's favor as to this factor regarding nonobviousness.

d. Failure of Others

Failure of others "to find a solution to the problem which the patent[] in question purport[s] to solve" is evidence of nonobviousness. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed. Cir. 1991) (internal quotation marks and citation omitted); *see also Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 876 F. Supp. 2d 295, 417 (S.D.N.Y. 2012) ("The repeated failure of others to solve a problem addressed by an invention is further confirmation of the invention's non-obviousness."). The purpose of such evidence "is to show indirectly the presence of a significant defect in the prior art, while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1082 (internal quotation marks and citation omitted). "In the pharmaceutical industry, the failure of others to develop a safe and effective drug often supports the nonobviousness of a drug that finally achieves success." *Teva*, 876 F. Supp. 2d at 417.

The "failure of others" analysis first requires the Court to define the problem that the patent purports to solve, since objective criteria such as this "help[s] turn back the clock and place the claim[] in the context that led to [its] invention." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). To this end, the Federal Circuit has cautioned against "us[ing] the invention to define the problem that the invention solves." *Id.* at 1377. Teva disputes that there was a "failure of others" here because it argues that the '244 Patent purported to solve the problem of "the creation of a nucleoside analog with 'antiviral activity'"—a problem that "had already been solved" by molecules created before entecavir's invention (including 2'-CDG, Madhavan 30, and others). (D.I. 151 at 58–59)

The specification of the '244 Patent states that the claimed compounds "are antiviral agents that can be used to treat viral infection in mammalian species such as domesticated animals . . . humans, and avian species." (JTX 1.0003) The specification discloses that the compounds are effective against certain viruses (including HSV-1 and HSV-2), for which it presents corresponding *in vitro* data, and then states that the compounds are "believed to be active against" a number of additional viruses, including hepatitis B. (*See generally* JTX 1) The patent does not include any hepatitis B *in vitro* data, as BMS did not even possess a hepatitis B assay until approximately four years after the October 1990 priority date of the patent.

Certainly, Teva is correct that if the "problem the patent purports to solve" is the identification of "antiviral agents" that are effective in treating viral infection in humans (such as HSV-1 and HSV-2, for which the patent contains certain test results), there was not a failure of others to develop such agents. Here, the Court looks to the language of the patent specification[42] for guidance. In so doing, the Court notes that it is skeptical that the "problem the patent purports to solve" can be said to be the development of an effective treatment for hepatitis B—as the patent contains no test data regarding hepatitis B, notes only that the antiviral agents discovered are "believed" to be active against hepatitis B, and mentions hepatitis B as just one of a number of such diseases that might possibly be affected by these agents. It also seems incongruous to attribute this as a focus of the patent, when BMS itself would not learn for years that entecavir demonstrated the kind of effectiveness against hepatitis B that it was later found to

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[42] *Cf. Janssen Pharm., Inc. v. Watson Labs., Inc.*, Civil Action No. 08-5103 (SRC), 2012 WL 3990221, at *21–22 (D.N.J. Sept. 11, 2012) (looking to the claim language and the patent specification to determine the inventor's understanding of the invention in this context).

possess. Nevertheless, the patent does at least call out hepatitis B as a disease that BMS had reason to believe would be affected by these agents. In light of that, the Court will consider BMS's argument that the patent purports to solve the problem of the need for an effective hepatitis B treatment.

Yet even in doing so, the Court does not find the proffered evidence to be strong. That is because BMS focuses its "failure of others" argument on the time period from entecavir's invention onward, arguing that the history regarding hepatitis B drugs is "littered with failures," while entecavir has been a success, thus helping to prove its nonobviousness. (D.I. 150 at 86–87) In support of its "littered with failures" claim, BMS points primarily to a 2003 Hepatitis B Foundation newsletter charting sixteen compounds then in clinical development for the treatment of hepatitis B. (JTX 48.0007) It asserts that the list is indicative of this history of failure since "[t]welve of the molecules on that list failed." (D.I. 150 at 86) Furthermore, BMS contends that "failure" for purposes of this analysis extends beyond that list, because (1) it is not comprehensive, as additional molecules were explored both before and after 2003 (including 2'-CDG), and (2) many of the drugs that have since received FDA approval are problematic. (*Id.* at 86–87)

This evidence does not paint a dramatic picture of failure in terms of effective treatments for hepatitis B. Rather, it highlights that *numerous* drugs for the treatment of hepatitis B have been developed and approved by the FDA. In looking at the very 2003 chart put forward by BMS, one sees that a quarter (four) of the nucleoside analogs on the chart became FDA-approved

and were used to successfully treat hepatitis B in many patients. (Tr. 1350:2-7; 1413:4-7)[43] A fifth drug, tenofovir, which was later approved to treat hepatitis B, is not even listed on the chart. (Tr. 1430:7-11) As to the remaining asserted "failures" on the chart, there is little evidence, as Dr. Gish testified only as to the specific reasons why three of the other twelve compounds did not make it to market. One of them, FTC, is now sold in a combination pill with tenofovir to treat HIV. (Tr. 1347:14–18; *see also* 457:16–21) Another is approved for the treatment of hepatitis B in other countries. (Tr. 1348:20–1349:2; *see also* 458:1–4) Dr. Gish did not know what happened to nearly all of the remaining nine compounds on the chart, or why they did not make it to market (including whether it was due to a failure to demonstrate significant antiviral activity, or for some other reason). (Tr. 1429:3–1430:6) In sum, the record from the chart BMS put forward as its primary evidence of a litany of failure in this area does not strongly support that argument, as it contains a number of drugs ultimately approved to treat hepatitis B (and many for which there was little or no evidence as to their inability to treat hepatitis B, other than the fact that they never obtained FDA approval).

Indeed, Teva's expert, Dr. Thio, testified that the time period from 1998–2008 saw an "explosion" of hepatitis B treatments in a "relatively short period of time." (Tr. 420:23–421:1) Even BMS's own expert Dr. Gish referred to this decade as a "dynamic" time in this regard, acknowledging that it was a time of "huge change." (Tr. 1413:4–14; 1431:5–11) Other leading experts in the hepatitis B community have agreed with Drs. Thio and Gish, viewing the drug development history for hepatitis B as a success, not a failure. For instance, one May 2007

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[43] *Cf. Otsuka*, 2010 WL 4596324, at *25 (finding sufficient evidence of failure of others where "the FDA did not approve a single new antipsychotic drug between loxapine in 1975 and clozapine in 1990" despite years of active research).

article concluded that "[s]ignificant advances in the management of chronic hepatitis B (CHB) have been made over the past decade. . . . due to the introduction of effective antiviral therapy." (DTX 49) Similarly, a May 2011 article reported that "[s]ubstantial progress has been made in the treatment of hepatitis B in the past decade. The availability of medications that have potent antiviral activity and are safe for use in patients with cirrhosis has broadened the indications for hepatitis B treatment." (DTX 76.0001) The real-world evidence, bolstered by expert testimony, stands in contrast to BMS's assertion that the drug development history for hepatitis B is "littered with failures." (D.I. 150 at 86)

These facts do not set forth persuasive proof of a "failure of others" to solve the problem that the '244 Patent purports to solve (even if that "problem" can be read very broadly to include effectively treating hepatitis B). Nor do they illustrate the failure of competitors to "create a therapeutically effective product." (*See* D.I. 156 at 15 (internal quotation marks omitted)) Thus, the Court finds that the proffered evidence regarding "failure of others" fails to persuasively demonstrate that entecavir was not obvious.

e. Long-felt But Unmet Need for the Claimed Invention

Another objective indication of nonobviousness that BMS relies upon is a long-felt but unmet need for the claimed invention. "Long-felt need is closely related to the failure of others. Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1082.

BMS focuses its main arguments here on the time of entecavir's launch in 2005, arguing that the shortcomings of the three FDA-approved drugs that existed at that time could not meet

the needs of most patients, and thus entecavir satisfied a long-felt but unmet need for a "safe, effective long-term treatment for hepatitis B that did not have disabling side effects or high levels of resistance." (D.I. 156 at 17–18; *see also* D.I. 150 at 88-89) In response, Teva asserts that there was no long-felt, unmet need for a compound with antiviral activity—what it views to be the problem solved by the invention. (D.I. 151 at 60–62; D.I. 157 at 41–42) Moreover, Teva argues that BMS has failed to prove a long felt but unmet need for a hepatitis B treatment because of the existence of all the other previously-referenced drugs that have met that need, many before entecavir did (including tenofovir, a comparable first-line therapy like entecavir). (D.I. 151 at 60–62; D.I. 157 at 41–42)

The Federal Circuit has recently explicitly stated that a court is to assess whether a long-felt and unmet need existed as of the "filing date of the challenged invention," not as of "the time the invention becomes available on the market, when it can actually satisfy that need." *See Procter & Gamble Co.*, 566 F.3d at 998; *see also Plumley v. Mockett*, 836 F. Supp. 2d 1053, 1072 (C.D. Cal. 2010) ("Evidence that an invention satisfied a long-felt and unmet need that existed on the patent's filing date is a secondary consideration of nonobviousness.") (citing *Procter & Gamble Co.*, 566 F.3d at 998). In light of this clear, recent guidance from the Federal Circuit, the court feels compelled to assess the "long-felt and unmet need" prong as of October 1990.[44]

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[44] Were it to address the history after entecavir's invention through to the present day, the Court would find the evidence of long-felt need to be mixed. It could not be said that, in 2005, entecavir met a long-felt need for the treatment of hepatitis B in oral form, as a number of drugs had met that need. Nor could it be said that entecavir was the first drug to meet such a need with few resistance issues and high potency, as tenofovir has similar properties and was used by patients years before entecavir (though only by a smaller number of co-infected patients). And it is difficult to characterize the need for an effective hepatitis B drug with these attributes as

In October 1990, the patent's filing date, hepatitis B was considered an important worldwide disease (much as it is today), though it was not considered a major cause of death or illness in the United States and other developed countries. *See supra* ¶¶ 161-62. At this time, there was no FDA-approved drug for the treatment of hepatitis B. It was not until 1991, a short while after entecavir's invention, that standard interferon came to market, the first FDA-approved drug for the treatment of chronic hepatitis B. (Tr. 418:5-8; 1336:8-12) So, in this sense, there was a long-felt need for a drug that could be effective against hepatitis B at that time entecavir was invented (a need that had not been met by any available drug that was actually in use).

However, it is worth noting that at least three other drugs were invented before entecavir that went on to gain FDA approval and be used with significant success to treat hepatitis B (adefovir, tenofovir, and lamivudine). *Cf. Eli Lilly and Co. v. Zenith Goldline Pharm., Inc.*, 364 F. Supp. 2d 820, 906 (S.D. Ind. 2005) (finding that the drug-at-issue satisfied the long-felt need for a safe, atypical antipsychotic where the priority date for the patent was April 1990 and the drug covered by the patent was not approved for use until 1996, despite fact that a second drug was prescribed to the relevant population beginning in February 1994, as there was no record evidence showing that the second drug was "invented or patented" before the drug covered by the patent). Therefore, while there was clearly a long-felt but unmet need for an effective hepatitis B

"long-felt," because up through 2005, the time of entecavir's launch, in view of the consecutive success of lamivudine and adefovir, no such "long-felt" need had been understood to exist. At most, it could be said that entecavir was the first FDA-approved drug to treat hepatitis B that had such significant potency and good properties against resistance (though tenofovir, with similar qualities, was approved three years later in 2008). To state these facts is to acknowledge the crowded field that entecavir joined as to hepatitis B treatment in the 2000s.

treatment as of October 1990, and entecavir theoretically satisfied that need (though BMS would not know that until four years later, in 1994, when it began testing entecavir against hepatitis B), so did these three other compounds. None of these compounds, including entecavir, were used to treat patients until several years after their inventions.

f. Unexpected Results

A showing by a patentee that the claimed invention exhibits some "superior property or advantage" that the skilled artisan would have found "surprising or unexpected" supports the conclusion that the invention was not obvious to the skilled artisan. *In re Soni*, 54 F.3d at 750; *Eli Lilly*, 364 F. Supp. 2d at 907. The reasoning behind this notion is "'that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious.'" *Id.* (quoting *In re Mayne*, 104 F.3d at 1343). The Federal Circuit has instructed that "in order to properly evaluate whether a superior property was unexpected, the court should [] consider[] what properties were expected." *Pfizer*, 480 F.3d at 1371.

"In order for a showing of unexpected results to be probative of nonobviousness, such evidence must at least establish that: (1) there actually is a difference between the results obtained and those of the closest prior art, and (2) the difference actually obtained would not have been expected by one skilled in the art at the time of the invention." *Eli Lilly*, 364 F. Supp. 2d at 907 (citing *In re Freeman*, 474 F.2d 1318, 1324 (C.C.P.A. 1973)). "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Eli Lilly*, 364 F. Supp. 2d at 907 (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)). Evidence of unexpected results "may be [considered] even if that evidence was obtained after the patent's filing or issue date." *Genetics*

Inst., LLC v. Novartis Vaccines and Diagnostics, Inc., 655 F.3d 1291, 1307 (Fed. Cir. 2011); *see also Galderma Labs.*, 2012 WL 4169686, at *50.

BMS argues that entecavir's "superior clinical benefits" including "unprecedented potency, high efficacy, rare resistance and excellent safety" are unexpected results that help show the nonobviousness of entecavir. (D.I. 150 at 81–84; D.I. 156 at 13–15) Teva responds that entecavir's properties, while positive, were not unexpected, and that BMS has not presented any evidence to the contrary. (D.I. 151 at 62–64; D.I. 157 at 42–45)

In analyzing whether entecavir exhibited unexpected superior results, the Court must first analyze what properties of entecavir were expected. The record shows that BMS expected that entecavir would have some antiviral activity against hepatitis B, as the '244 Patent, issued before entecavir was tested against hepatitis B, stated that the compound was believed to be effective against a variety of viruses, including hepatitis B. (JTX 1.0003, col. 4:34–42) This belief was based on Dr. Zahler's "scientific judgment." (Tr. 637:9–11) Once BMS did develop a hepatitis B assay in 1994, Dr. Zahler was asked to select "a limited number" of BMS's compounds; entecavir was among those that he chose. (Tr. 638:18–641:10) In fact, when the compound could not be found in storage, Dr. Zahler testified that he "strongly encouraged" BMS employees to keep looking and even joined in the hunt himself. (Tr. 832:10–13) Dr. Zahler testified that his excitement came from the fact that an adenine analog recently tested came in "quite potent" against the hepatitis B virus, but also showed some toxicity. (Tr. 832:13–16) Dr. Zahler was "optimistic," based on BMS's prior work, that entecavir would show activity that was "at least equipotent" and he "certainly . . . felt it would be less toxic." (Tr. 832:17–22) Thus, Dr. Zahler was "eager" to get the molecule tested against hepatitis B. (Tr. 832:23–24)

This testimony illuminates the properties that a person of skill in the art would have expected entecavir to demonstrate—something equal to or better than "quite potent" activity against hepatitis B and low toxicity. Although BMS argues that "[n]o one predicted, or could have predicted" entecavir's properties, this testimony, coupled with the description in the patent's own specification, suggests that at least these basic properties could have been predicted at the time of entecavir's invention. *Cf. Procter & Gamble Co.*, 566 F.3d at 997 (finding evidence of unexpected results where the plaintiff's witnesses consistently testified that the drug's properties were not expected); *Teva*, 876 F. Supp. 2d at 418 (finding evidence of unexpected results where scientists involved in the development of the drug-at-issue were surprised by testing results showing low toxicity of that drug). And there were examples in the prior art, at the time of the invention, of compounds that also showed effectiveness against hepatitis B without known toxicity issues, including 2'-CDG. So these results were not unexpected.

Entecavir has turned out to have certain attributes beyond what was expected at the time of the invention. For example, it ultimately showed "extraordinary potency against" the hepatitis B virus. (Tr. 1036:2–8) Dr. Zahler testified that he did not anticipate that the dosage necessary for entecavir to inhibit the replication of a cell line to be "[s]o low" (and thus its potency to be quite as strong as it turned out to be). (Tr. 833:9-835:2; *see also* Tr. 1097:17-1098:21; 1251:5-8) Entecavir is more potent *in vitro* than every other compound, a fact that Dr. Thio acknowledged. (JTX 107.0003–.0004; Tr. 492:17–19 ("In vitro, entecavir is more potent than all of the other nucleotide and nucleosides")) Entecavir's *in vivo* potency is also strong (though the drug has not ultimately turned out to be "superior" to all others that later came to market, as it has a

comparable potency to tenofovir). (Tr. 1358:22–1360:17; DTX 238.0004; *see also* Tr. 834:17–835:2)

Entecavir has also turned out to have a very high genetic barrier to resistance, as resistance to the drug develops slowly, the magnitude of which Dr. Schneller called unexpected. (Tr. 1098:1-21; 1415:10-1416:9; DTX 107.0003; DTX 238.0014; DTX 237.0005) Its resistance profile ultimately was found to show "superior" resistance properties to all other drugs that later came to market, though not as to tenofovir—as to both drugs, such resistance is very rare. In a 2012 study, Dr. Gish concluded that "the drugs that have shown the highest barrier to resistance in clinical studies in NA-naive patients are entecavir and tenofovir." (DTX 237.0003)

Both parties' experts agree that entecavir is a very safe and effective drug, as has tenofovir turned out to be (as well as the other drugs that have received FDA approval for treatment of chronic hepatitis B). (Tr. 446:1-3; *see also* 1356:16–22) No witness testified that the safety of the drug would have been "unexpected." However, Drs. Schneller and Zahler also attested that entecavir has a large therapeutic window, meaning the range between the dose that effectively treats the hepatitis B virus versus the dose that displays toxicity. (Tr. 1097:17–1098:5; 833:7–24) Dr. Schneller testified that the size of this window could not have been expected during the time of entecavir's invention. (Tr. 1098 at 1-21)

Accordingly, the Court finds that some of the good results that entecavir ultimately demonstrated could have been predicted at the time of its invention, and, thus, were not unexpected. Other of those results (such as its high potency, high barrier to resistance and the size of its therapeutic window) appear to have been unexpected at that time (though many have

not been found "superior" to tenofovir). The Court finds the existence of these unexpected properties provides some support to BMS's argument as to nonobviousness.

g. Summary of Objective Considerations of Nonobviousness

Ultimately, as set forth above, the Court has found the evidence regarding objective considerations of nonobviousness to be mixed. As to some considerations, such as the commercial success that entecavir exhibited, whether there was a long-felt but unmet need for the claimed invention, or as to certain unexpected properties that it demonstrated, the Court has found there to be some evidence that could support of a finding of nonobviousness (though in these cases, the record is more nuanced than BMS asserts). As to the other factors (including the impact of Teva's choice to copy entecavir, whether there has been a failure of others to find a solution to the problem that the '244 Patent purports to solve, or whether there was a demonstrated skepticism as to entecavir), the Court has not found the evidence put forward by BMS to be particularly compelling.

C. Conclusion Regarding Obviousness

Ultimately, the Court concludes that Teva has made out a strong *prima facie* case of obviousness. The evidence that it put forward at trial in that regard was multi-faceted and compelling. In addition, as to almost every significant portion of the *prima facie* case, Teva's position was not only bolstered by the opinion of its expert, Dr. Heathcock, but also by the testimony of BMS's expert, Dr. Schneller. On cross-examination, Dr. Schneller was forced to concede the accuracy of many significant points that Teva sought to assert as to that *prima facie* case. The force of this evidence was clear, and it was convincing.

As noted above, the evidence as to objective considerations was mixed. Some of those considerations redounded to the benefit of BMS's position as to nonobviousness to a degree, but as to a number of other considerations, the impact of that evidence was not particularly compelling. The totality of that evidence did not strongly persuade the Court as to entecavir's nonobviousness.

Taken together, particularly in light of the significant force of Teva's *prima facie* case, and the fact that the PTO was not able to consider certain material prior art references regarding 2'-CDG during prosecution of the patent, *see KSR*, 550 U.S. at 426, the Court finds that Teva has demonstrated by clear and convincing evidence that claim 8 of the '244 Patent is invalid as obvious under Section 103. *See Pfizer*, 480 F.3d at 1372 ("Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. Here, the record establishes such a strong case of obviousness that Pfizer's alleged unexpectedly superior results are ultimately insufficient.") (internal citations omitted).

II. INEQUITABLE CONDUCT

A. Legal Standard

To prevail on an inequitable conduct claim, a defendant must establish both the materiality of the withheld reference and the applicant's intent to deceive the PTO. *Therasense, Inc. v. Becton, Dickinson and Co.*, 649 F.3d 1276, 1290 (Fed Cir. 2011) (en banc). In *Therasense*, the Federal Circuit rejected the "sliding scale" approach to proving inequitable conduct, "where a weak showing of intent may be found sufficient based on a strong showing of materiality, and vice versa." *Id.* Instead, *Therasense* made clear that "[i]ntent and materiality are

separate requirements." *Id.* Moreover, a district court may not infer intent solely from materiality, and thus "[p]roving that the applicant knew of a reference, should have known of its materiality, and decided not to submit it to the PTO does not prove specific intent to deceive." *Id.*

With respect to materiality, the standard is but-for materiality unless there is affirmative egregious misconduct (which is not alleged here). *Id.* at 1291-92. A prior art reference "is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art." *Id.* at 1291. In the inequitable conduct context, but-for materiality must be shown by a preponderance of the evidence, "giv[ing] claims their broadest reasonable construction." *Id.* at 1291-92; *see also Aventis Pharma S.A. v. Hospira, Inc.*, 675 F.3d 1324, 1334 (Fed. Cir. 2012). "Often the patentability of a claim will be congruent with the validity determination—if a claim is properly invalidated in district court based on the deliberately withheld reference, than that reference is necessarily material because a finding of invalidity in a district court requires clear and convincing evidence, a higher evidentiary burden than that used in prosecution at the PTO." *Therasense*, 649 F.3d at 1292.

To satisfy the intent requirement, "the accused infringer must prove by clear and convincing evidence that the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it." *Id.* at 1290; *1st Media, LLC v. Elec. Arts, Inc.*, 694 F.3d 1367, 1374-75 (Fed. Cir. 2012) ("Knowledge of the reference and knowledge of materiality alone are insufficient after *Therasense* to show an intent to deceive. . . . To sustain a charge of inequitable conduct, 'clear and convincing evidence must show that the applicant made a deliberate decision to withhold a known material reference.'"). Thus, inequitable conduct

requires clear and convincing evidence of a specific intent to deceive the PTO. *Therasense*, 649 F.3d at 1290. Because direct evidence of deceptive intent is rare, a district court may infer intent from indirect and circumstantial evidence. *Id.* However, "the specific intent to deceive must be the 'single most reasonable inference able to be drawn from the evidence.'" *Id.* at 1291 (quoting *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1366 (Fed. Cir. 2008)). "Indeed, the evidence must be sufficient to *require* a finding of deceitful intent in light of all of the circumstances." *Id.* (internal quotation marks and citation omitted). "Hence, when there are multiple reasonable inferences that may be drawn, intent to deceive cannot be found." *Id.* at 1290-91.

B. Discussion

Teva bases its inequitable conduct allegation on the fact that 2'-CDG was not cited to the PTO by Mr. Venetianer, Mr. Davis and Dr. Zahler. (D.I. 151 at 67) Teva argues that each of these three men had a duty to disclose 2'-CDG to the PTO, in that they were "acutely aware of 2'-CDG, its similarity to entecavir and its relevance to the patent application, [but] withheld all prior art regarding 2'-CDG during prosecution." (*Id.*) In its post-trial briefing, Teva asserts that Shealy 1984, the Shealy '255 Patent and Marquez (collectively referred to below as "the 2'-CDG prior art" or "the references") were the prior art references disclosing 2'-CDG that should have been, but were intentionally not disclosed by Mr. Venetianer, Mr. Davis and Dr. Zahler. (*Id.* at 37-45, 67-73)[45]

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[45] Although Teva listed the Shealy 1987 reference in its Amended Answer as another 2'-CDG-related reference that BMS failed to disclose to the PTO, (D.I. 54 at ¶¶ 7-52), and stated in the Pre-trial Order that it intended to prove that the reference was intentionally withheld from the PTO, (D.I. 135, ex. 2.2 at ¶ 28), Teva does not mention Shealy 1987 in the inequitable conduct sections of its post-trial briefing. The Court therefore understands Teva now

For the reasons discussed below, even assuming the but-for materiality of the references, Teva has not proven by clear and convincing evidence that these individuals committed inequitable conduct before the PTO.

1. Knowledge of the References, Knowledge of Materiality and Deliberate Decision to Deceive the PTO

a. Mr. Venetianer

With respect to Mr. Venetianer, Teva bases its assertion that he knew of the significance of 2'-CDG on the fact that during the prosecution of the '244 Patent, Mr. Venetianer was involved with certain applications on which Dr. Zahler was a named inventor, in which the 2'-CDG prior art was cited or was noted by the Examiner. (D.I. 151 at 70-71) More specifically:

> (1) In December 1988, Mr. Venetianer disclosed the 1984 Shealy article and the Shealy '255 Patent by listing them on information disclosure statements during prosecution of the '914 application (which led to the issuance of the '075 Patent);
>
> (2) In January 1989, during Mr. Venetianer's work with the prosecution of the '376 application, the Examiner rejected certain claims as obvious in light of Marquez;
>
> (3) Mr. Venetianer disclosed Marquez in the '375 application, and, after the PTO rejected certain claims as obvious in light of Marquez in October 1989, Mr Venetianer responded by noting that the compounds disclosed by Marquez had "antiviral activity."; and
>
> (4) In November 1990, during prosecution of the '957 application, the Examiner issued an office action rejecting certain claims as obvious over certain prior art, including the Shealy '255 Patent.

(Tr. 719:15-721:17; 724:12-725:11; DTX 159.0063-.0065; DTX 160.0001-.0005; DTX 2.0001, .0088, .0090, .0167 (reference J); DTX 164.0001, .0005; DTX 165.0005; DTX 167.0008; Tr.

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to have abandoned its assertion that this reference should be a part of the inequitable conduct calculus, and the Court thus will not address that reference further.

728:11-730:20) As Mr. Venetianer either provided these references to the PTO himself, or was the prosecuting attorney to whom the PTO cited the references in rejecting claims of certain applications, it can be inferred that Mr. Venetianer had knowledge of these references at some point in these time frames. (*See, e.g.*, Tr. 730:21-731:1 (Mr. Venetianer noting that he would have reviewed the Shealy '255 Patent after the rejection relating to the '957 application); 736:15-21 (Mr. Venetianer noting that it was his practice to review a PTO rejection with the inventor))

However, there is no other evidence in the record of Mr. Venetianer's level of familiarity with these references, nor that he considered them related to the '244 Patent application. While these other patent applications were filed or were under review by the PTO during the time leading up to and after the filing of the '244 Patent application, the applications were not directly related to the '244 Patent application.

Moreover, there is no evidence as to these other patent prosecutions that 2'-CDG was highlighted either by Mr. Venetianer or the Examiner in any specific way, nor is there any evidence that Mr. Venetianer otherwise had particular knowledge of or familiarity with 2'-CDG. Even in the applications where the 2'-CDG prior art was listed as the basis for a rejection by the PTO, the Examiner did not single out 2'-CDG as the basis for the rejection. For example, as to the rejections regarding the '376 application and the '375 application (and Mr. Venetianer's response to the Examiner as to the latter), the references to Marquez noted only the antiviral activity exhibited by carbocyclic nucleoside analogs generally, and did not call out 2'-CDG specifically. (DTX 160.0005; DTX 164.0005; DTX 165.0005) Similarly, with regard to the Examiner's rejection of the claims of the '957 application (which occurred in December 1990, just days before Mr. Venetianer left BMS), the Examiner, without referencing the Shealy '255

Patent by name, simply made reference to it as one of a group of "secondary references [that] teach antiviral activity." (DTX 3.0063)

Even if it can be assumed that, in conjunction with Mr. Venetianer's or the Examiner's few references to these documents, Mr. Venetianer would have reviewed them and had some occasion to familiarize himself with 2'-CDG, the evidence as to Mr. Venetianer's knowledge as to 2'-CDG's materiality to the '244 Patent application is not strong. With no evidence that Mr. Venetianer considered 2'-CDG in association with that application, no evidence that he had particular experience with 2'-CDG generally and only scant and circumstantial evidence that (over a period of years) he had association with documents that reference 2'-CDG, the Court does not believe that Teva has proven by clear and convincing evidence that he knew of 2'-CDG's materiality in this case.

Nor does the evidence suggest that Mr. Venetianer made a deliberate decision not to cite the 2'-CDG prior art to the PTO. In addition to the lack of evidence suggesting that Mr. Venetianer had a significant familiarity with 2'-CDG during the '244 Patent application, other factors suggest that he did not make a deliberate decision to deceive the PTO.

First, Mr. Venetianer's testimony established that the way he identified and obtained material prior art was not by locating such art on his own; instead, if he knew the inventors had been working in the area for a while and had been involved with other patent applications, he would ask those inventors to provide him with any relevant or close prior art. (Tr. 716:10-23; 733:16-24) Indeed, although he could not recall the process he utilized as to the '568 application with great specificity as of his deposition, Mr. Venetianer guessed that he had identified relevant prior art in that case in conjunction with the inventors. (Tr. 737:21-738:9) In that regard, the

evidence suggests that, based on the way Mr. Venetianer typically assembled prior art for a patent application, if the inventors of the '244 Patent did not point out a specific piece of prior art to him, he would have been unlikely to cite it to the PTO. And here, there is no evidence of record to suggest that Dr. Zahler or Dr. Slusarchyk actually did raise any of the references-at-issue with Mr. Venetianer prior to the submission of the '568 application or during the time that application was pending. This evidence suggests that Mr. Venetianer's failure to cite the 2'-CDG prior art was not due to a deliberate decision to withhold the references, but instead more likely because the references simply had not been brought to his attention by the sources whom he typically looked to for guidance.

Second, the contemporaneous evidence of record provides some support for the conclusion that Mr. Venetianer did not cite the 2'-CDG prior art in an effort to deceive, but instead because he was focused on certain characteristics that 2'-CDG did not possess. At the time of his deposition, Mr. Venetianer could not recall any specific discussion with the '244 Patent inventors about why Madhavan and other prior art references were cited to the PTO (while references including 2'-CDG were not). (Tr. 737:14-738:19; 739:7-11; 981:13-21) However, in an October 12, 1990 Information Disclosure Statement regarding the application, which identified the prior art that the applicants believed "may be material to the examination of this application and in respect of which there may be a duty to disclose," Mr. Venetianer wrote that:

> All of the attached references disclose antiviral compounds with exocyclic methylene double bonds. Applicants believe that [Madhavan] is the most relevant. Specifically, the Examiner's attention is directed to Compound 30 in the reference. . . .

(JTX 2.0107; JTX 2.0127, .0156-.0162) This document provides some support for the idea that when it came to relevant prior art, what the applicants (and Mr. Venetianer) were focused on was art disclosing compounds with an exocyclic methylene double bond—a characteristic that 2'-CDG does not have.

Third, although Mr. Venetianer could not recall much about the process relating to the '244 Patent application, he testified that, looking back, he surmised that he "tried to cite all of the relevant prior art" with regard to the application. (Tr. 979:17-18) Nothing about the substance of his answers or his appearance in providing those answers suggested to the Court that this explanation was less than truthful.

Fourth, there is another factor raised by BMS that relates to all three former BMS employees (including Mr. Venetianer), and which the Court finds supports the conclusion that Teva has not demonstrated deliberate deception of the PTO: that the motive to do so with respect to entecavir during the pendency of the '244 Patent application was particularly weak. That is, that during the entirety of the time of the pendency of the '244 Patent application, entecavir was not then seen as a drug likely to be particularly successful at BMS.

After Dr. Zahler conceived of entecavir and the compound was synthesized, it was then tested for antiviral activity; because of these modest results, entecavir was not further developed and was instead "put on the shelf" at BMS. (Tr. 827:12-829:4) Indeed, entecavir was not tested against hepatitis B at that time, because BMS did not have a hepatitis B assay. (Tr. 828:6-15) Because of this, according to Mr. Davis, at the time of its prosecution, the '244 Patent application had no more than a "middle priority" at BMS (and was not a "high priority"), since BMS had not identified an agent in that family that was likely to be a commercial success. (Tr. 923:9-18)

It was not until years later, in late 1994, that entecavir was tested against hepatitis B. (Tr. 829:10-830:15) Even at that point, it took BMS employees time to locate the lost sample of entecavir in BMS's storage facility, which was only found after a significant search. (Tr. 831:17-833:1) Only through the results of this testing was entecavir found to be very potent and effective against hepatitis B. (Tr. 833:7-838:4) Thus, the testing of entecavir against hepatitis B and the discovery of its effectiveness against that disease came well over a year after the April 1993 issuance of the '244 Patent. (Tr. 841:19-22)

This evidence diminishes the argument that one of the three then-BMS employees-at-issue (including Mr. Venetianer) would have been motivated to intentionally withhold the 2'-CDG prior art, in order to obtain the patent. Of course, it can be said (as Teva argues) that there is always motive to obtain a patent on particular compounds, (D.I. 157 at 52), and that the true value of such patents can sometimes not be realized until years later.[46] But here, it is less persuasive to argue that Mr. Venetianer (and the others) were motivated to deliberately deceive the PTO in order to obtain the '244 Patent, when the compound protected by that patent that is at the heart of this case (entecavir) was not seen by BMS as particularly important during that time

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[46] Teva also argues that in making this argument, "BMS implies that [Dr.] Zahler and the attorneys were more careless in complying with their duties of candor because the application simply was not that important." (D.I. 157 at 52) The Court does not take this to be the import of BMS's assertion. Instead, the Court understands BMS to simply be noting that its former employees are accused of misconduct—the deliberate deception of the PTO. It stands to reason that if individuals are accused of such an act, one that might bring with it significant consequences if uncovered, one might assume that the prospect for an outsized reward (if successful) would be a motivation for such conduct. And here, such a reward as to entecavir could not have been foreseen from 1990 to 1994, in that the drug was not seen at BMS as likely to produce significant commercial success during that time.

period—so much so that BMS put the compound "on a shelf" for years and nearly lost the compound in a storage facility.

2. Mr. Davis

With respect to Mr. Davis, the Court also finds, first, that Teva has not sufficiently proven that he knew that references to 2'-CDG were material to the application. As it did with Mr. Venetianer, Teva focuses on the fact that Mr. Davis had cited the 2'-CDG prior art at various times during the pendency of the '244 Patent application, with regard to other unrelated applications on which Dr. Zahler was listed as an inventor. These citations included: (1) Mr. Davis's February 1991 filing of the '823 application, in which he disclosed the Shealy 1984 article and Marquez as prior art, and the inclusion of the Shealy '255 Patent in the file history of that application, (Tr. 691:20-694:19; 695:19-696:11; DTX 4.0420, .0422, .0437, .0438); (2) his April 1991 correspondence with the Examiner regarding the '957 application, in which he attempted to distinguish the Shealy '255 Patent to the Examiner and referenced antiviral activity associated with carbocyclic analogs, (DTX 168.0001, .0012); and (3) his 1991 filing of the '391 application, in which he listed Shealy 1984 and Marquez to the PTO as being relevant prior art. (DTX 5.0431, .0457, .0469, .0473) Mr. Davis acknowledged that if he had cited certain prior art to the PTO, that meant that he had at some point reviewed those references; thus, Mr. Davis had knowledge of the references at some point during the pendency of the '244 Patent application. (Tr. 694:11-19)

As was the case with Mr. Venetianer, however, aside from these few associations with the 2'-CDG prior art, there was no other evidence put forward regarding Mr. Davis' work with, or familiarity with, these references. Indeed, unlike Mr. Venetianer, who had worked on patent

applications in this subject area regularly, when Mr. Davis took over the prosecution of the '244 Patent in December 1990, it was one of the first cases in the antiviral and nucleoside area that he had ever worked on; thus, it took him time to get up to speed on such applications. (Tr. 925:1-24) With little past history with the subject matter prior to the time period in question, and only a few documented instances in which Mr. Davis reviewed this art, the Court finds it less likely that Mr. Davis would have had such a grasp on the subject matter of the art that he would have been sure to know of its materiality.

Additionally, the number of patent applications that Mr. Davis was prosecuting during this time period further puts these citations in perspective, indicating that his work on the '244 Patent application was but a small part of a much larger whole. At the time, Mr. Davis was prosecuting applications regarding approximately 60 patent families (involving both U.S. and foreign applications). (Tr. 699:19-23; Tr. 711:11; 918:3-17) While he testified that he might occasionally find overlap between his work on one application and work he had previously done on another, in the main, he could not and did not focus on all 60 cases at once—and indeed would often go months without picking up a particular application file. (Tr. 921:12-922:16) In light of this workload, Mr. Davis' citation to the 2'-CDG prior art on a few occasions in 1991 (along with, even in those cases, many other pieces of prior art), takes on a diminished significance. Absent more significant and sustained interaction with the content of those references, the evidence does not suggest that Mr. Davis would have clearly called the references to mind as material to the '244 Patent application.

This conclusion is further strengthened by the fact that, with regard to the other prosecutions in which Mr. Davis referenced the 2'-CDG prior art, he did not do so in a way that

highlighted 2'-CDG specifically, nor that suggested that he had particular knowledge of or familiarity with 2'-CDG. In each case, the references to the prior art, at most, simply noted that the art disclosed certain carbocyclic nucleoside analogs that had been found to have antiviral activity, without calling out 2'-CDG for particular attention. (DTX 4.0421, .0438; DTX 168.0001, .0012; DTX 5.0431, .0457, .0469, .0473)

Additionally, Teva has not sufficiently proven that Mr. Davis made a deliberate decision not to cite the 2'-CDG prior art to the PTO. In addition to the lack of evidence suggesting that Mr. Davis had a significant familiarity with 2'-CDG during the '244 Patent application, other factors support this conclusion.

First, as did Mr. Venetianer, Mr. Davis explained that one significant way that he obtained prior art to cite to the PTO was by seeking out that information from the inventors. (Tr. 711:12-712:5) Indeed, as to the prosecution of the '244 Patent application, he recalled meeting with the inventors many times and asking them to produce relevant prior art, (Tr. 712:6-18), and there is no evidence to suggest that the inventors identified any of the 2'-CDG prior art to Mr. Davis during these interactions. Mr. Davis' testimony made the nature of his reliance on the inventors in this process clear, when he agreed that if the inventors had told him that "2'-CDG was more relevant to the '244 Patent [application than the references that were cited, he] would have cited 2'-CDG" to the PTO. (Tr. 702:18-22; 713:5-9) Although it is of course possible that Mr. Davis could have identified the 2'-CDG prior art on his own as material, the fact that he tended to rely in significant part on the inventors to identify such art (and that they did not do so here) makes it less likely that he made a deliberate decision to withhold those references from the PTO.

Second, the fact that the '244 Patent application was but one of a large number of matters on Mr. Davis' desk during the early 1990s renders it less likely that he made a deliberate decision to withhold the references. Instead, it supports the notion that the 2'-CDG prior art references were not front of mind for him in relation to the '244 Patent application—in that they were just three of many references that he dealt with over a period of years spent working on numerous different patent applications.

Third, Mr. Davis himself clearly stated that he did not make a deliberate decision to deceive the PTO and he did so with a clarity and candor that the Court found convincing. (Tr. 702:1-5; 946:3-13; *see also* 704:20-705:4 ("I didn't look at Shealy and say, no, I'd better not cite that. It's too close.")) Mr. Davis explained that he knew that if he were to be found to have committed inequitable conduct before the PTO while at BMS, this would invalidate the patent-at-issue, could lead to his disbarment before the PTO and could lead to the termination of his employment at BMS. (Tr. 944:11-945:6) He explained that, to him, it would not "make sense to" withhold references like the 2'-CDG prior art, both because the references were public documents and would later likely come to light, and because inclusion of the references could have "strengthen[ed]" the patent (had the patent been issued over the cited references). (Tr. 702:12-22; 945:7-23)

Moreover, Mr. Davis explained that while he may have had knowledge of these references (in the sense that he had cited them before regarding other applications), the reason he did not cite them here was that they were not "in front of [him]" or brought to his attention during the prosecution-at-issue. (Tr. 700:5-6; 701:22-703:17; *see also* Tr. 711:2-7) Indeed, Mr. Davis was candid, stating that looking back on it now, he "would have cited" these references to

the PTO if they *had* been brought to his attention, or if he had been thinking about them at the time of the '244 Patent application. (Tr. 702:6-17) Mr. Davis acknowledged that this was because there were similarities between 2'-CDG and entecavir—particularly the fact that "2'-CDG had "a five-membered ring and it has the hydroxy methyl and the hydroxy group on it." (Tr. 702:23-703:5) Having observed Mr. Davis' testimony in this regard, the Court found that testimony credible—testimony that strengthens the Court's conclusion that Mr. Davis did not make a deliberate decision not to cite the prior art-at-issue, but instead simply was not thinking of the references as to this application.

Fourth, Mr. Davis' contemporaneous correspondence with the Examiner tends to support his claim that, when it came to prior art relating to the '244 Patent application, he was not thinking about 2'-CDG, but instead was focused on other types of compounds. In submitting his September 1991 Information Disclosure Statement as to the "most relevant art" relating to the application, Mr. Davis listed compounds that each had an exocyclic methylene group attached to the five-membered ring of the sugar portion of the compound. (JTX 3.0018; Tr. 926:9-16) In subsequent correspondence with the Examiner regarding the Examiner's initial rejection of certain claims in light of another piece of prior art, the EP '849 application, Mr. Davis (and the Examiner) discussed whether the EP '849 application disclosed structurally similar compounds, in that those compounds contained such an exocyclic methylene group. (Tr. 681:24-686:20; JTX 3.0333; JTX 3.0340-42) This evidence bolsters Mr. Davis' explanation that, at the time, he was not thinking of 2'-CDG, in that 2'-CDG did not have an exocyclic methylene group attached to it.

Lastly, as noted above, the motive for Mr. Davis to deliberately deceive the PTO in this way was weak, in light of BMS's lack of interest in developing entecavir during the pendency of the '244 Patent application.

3. Dr. Zahler

With respect to Dr. Zahler, Teva focuses its arguments on the two Shealy references, Shealy 1984 and the Shealy '255 Patent, which Dr. Zahler undisputedly had knowledge of prior to the time of the '244 Patent application.[47] (Tr. 540:7-541:12; 548:10-16; D.I. 157 at 47) The Court finds, however, that even if the other portions of the test for inequitable conduct could be met as to Dr. Zahler (i.e., that he knew of the references and that he knew of their materiality), Teva has not clearly and convincingly demonstrated that he made a deliberate decision not to cite these references. The Court comes to this conclusion for a number of reasons.

First, there has certainly been no direct evidence presented that, in the context of the prosecution of the '244 Patent application, Dr. Zahler contemplated the 2'-CDG prior art and then made a deliberate, intentional decision not to cite that prior art to the PTO for any reason, let alone with the intent to deceive the PTO.

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[47] Teva refers to the two Shealy references as the "key" references in the inequitable conduct inquiry, perhaps because 2'-CDG is mentioned by name in the Shealy references (and not in Marquez) and is mentioned far more prominently in the Shealy references than it is in the Marquez reference. As to the Marquez reference, there was no direct evidence at trial that Dr. Zahler knew of the reference during the relevant time period. Marquez was cited, however, in various patent applications submitted by Mr. Venetianer or Mr. Davis—applications on which Dr. Zahler was a inventor—or in rejections by the PTO regarding such applications. (D.I. 151 at 42, 44) Teva appears to base its assertion as to Dr. Zahler's knowledge of Marquez on these facts, and Mr. Venetianer's and Mr. Davis' statements that they discussed prior art cited in an application or in a rejection by the Examiner with the inventors associated with those applications. (*See, e.g.*, Tr. 517:6-15; 523:7-14; 711:12-712:5; 716:10-18; 733:16-24; 736:12-24; 843:1-20; 844:9-15)

Second, the evidence is undisputed that Dr. Zahler was not thinking of 2'-CDG when he conceived the initial structure for entecavir, nor did 2'-CDG play a role in that process (although it was later used as part of BMS's computer modeling effort regarding entecavir). (Tr. 542:6-12; 546:3-9; 854:8-859:22; 864:5-865:1; 881:6-9) Instead, Dr. Zahler was inspired by the natural 2'-deoxyguanosine and by lobucavir in thinking of entecavir's structure. (Tr. 542:18-543:23; 803:9-804:8; *see also* Tr. 651:20-652:2; 959:21-960:3; 962:2-9; 962:20-963:1; 967:13-18) Had 2'-CDG spurred Dr. Zahler to first conceive of entecavir, it would be easier for Teva to argue that Dr. Zahler must have made a deliberate decision to withhold references relating to 2'-CDG.

Third, Dr. Zahler's explanation for why the 2'-CDG prior art was not cited to the PTO regarding the '244 Patent application was that during this time, he believed the utilization of the exocyclic methylene group to be the most important feature of entecavir's structure. (Tr. 846:15-849:11) While Dr. Zahler did note that he understood that structurally similar compounds to the compounds referenced in an application would be material to the PTO, (Tr. 525:1-13; 526:13-527:8), he also explained that when he examined possible prior art for an application, he tended to focus on the primary feature of the invention—the one that was "most distinguishing"—and to provide prior art that contained that feature. (Tr. 845:2-6) And he explained that, to him, the exocyclic methylene group in entecavir is the "most distinguishing" feature of that invention. (Tr. 846:19) And indeed, the exocyclic methylene group clearly is an important feature of entecavir, for reasons discussed throughout this Opinion.

Moreover, Dr. Zahler's explanation that he was most focused on the exocyclic methylene group when examining prior art mirrors the way in which BMS corresponded with the PTO. BMS cited to Madhavan compound 30 as that "most relevant" piece of prior art in its application,

and that compound did in fact contain an exocyclic methylene group at the 5 prime (or 6 prime) position; indeed, at the time, Madhavan was the only piece of art that referenced an exocyclic methylene group at that position. (Tr. 308:13-309:1; 849:12-850:5; 881:10-19) Each of the other references cited in the application also contain an exocyclic methylene group attached to the five-membered ring of certain compounds referenced in those documents. And, of course, 2'-CDG lacks an exocyclic methylene group, rendering it different from these references in this respect. (Tr. 936:20-22; DTX 126.002; JTX 1.0028) Therefore, the reason given by Dr. Zahler in not citing to the 2'-CDG prior art is supported by the content of the references BMS *did* choose to cite.

In addition, testimony of other BMS employees regarding the application corroborates Dr. Zahler's asserted rationale for not considering the 2'-CDG prior art at the time. Mr. Davis, for example, testified that he too believed at the time of the application that the most important structural feature of the claims of the '244 Patent was the existence of the exomethylene group on the cyclopentyl ring (and that Madhavan was therefore the most relevant piece of prior art). (Tr. 926:20-927:2; 926:9-928:21; 932:1-9) Neither Mr. Davis or Mr. Venetianer contradicted Dr. Zahler's claim that he was not thinking of 2'-CDG in relation to the entecavir application, nor Dr. Zahler's claim that 2'-CDG was not discussed during that process.

Finally, as was previously noted, Dr. Zahler's motive to deliberately deceive the PTO was not strong, in light of BMS's lack of interest in developing entecavir during the pendency of the '244 Patent application.

4. Whether the Single Most Reasonable Inference to Be Drawn From the Evidence Is That Mr. Venetianer, Mr. Davis or Dr. Zahler Had the Specific Intent to Deceive the PTO

The Court, taking into account its conclusions above, finds that Teva has not demonstrated that the single most reasonable inference in this case is that Mr. Venetianer, Mr. Davis or Dr. Zahler had the specific intent to deceive the PTO, nor that the evidence requires a finding of deceitful intent in light of all of the circumstances. In this case, it is as reasonable, if not more reasonable, to infer that these men had made a determination that the most important feature of entecavir was the addition of an exocyclic methylene group to the five-membered ring—and that, because they were focused on that feature, they went on to cite prior art to the PTO that referred to compounds containing that type of substitution (and not to 2'-CDG, which did not). Moreover, at least as to Mr. Venetianer and Mr. Davis, it is also just as reasonable, if not more reasonable, to infer that another reason why they did not cite these references was because the references had not been brought to their attention by the inventors, and these men would have had little reason to have identified the prior art as relevant on their own.[48]

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[48] In its post-trial briefing, Teva relies on *Aventis Pharma S.A. v. Hospira, Inc.*, 675 F.3d 1324 (Fed. Cir. 2012) for its assertion that, as in that case, the former BMS employees here engaged in "selective disclosure" when they cited the 2'-CDG prior art references to the PTO in other applications, but not the '244 Patent application. (D.I. 151 at 71) The Court agrees with BMS that the facts in *Aventis* were not similar to those here. In *Aventis*, as to the first withheld reference, there was, *inter alia*, testimony from the inventor and contemporaneous internal company memoranda indicating that information disclosed in the withheld reference was one of the "main factors that shaped" the inventor's thinking in arriving at the invention. *Aventis*, 675 F.3d at 1335. Similarly, as to the second withheld reference in *Aventis*, the inventor testified that he was dissatisfied with a brochure for the drug-at-issue because it did not list the reference (and affirmatively took steps to include the reference in the brochure) but when submitting the patent application, the inventor failed to disclose that same reference. *Id.* at 1336. Here, in contrast, there is not similar evidence that 2'-CDG was a main factor for Dr. Zahler in conceiving of entecavir, and there not the same type of contemporaneous evidence as to Dr. Zahler's own personal and intentional inclusion of references to 2'-CDG in internal BMS documents relating to entecavir (while at the same time failing to disclose 2'-CDG to the PTO as to the entecavir patent application).

5. Conclusion

For these reasons, the Court finds that Teva has not demonstrated by clear and convincing evidence that Mr. Venetianer, Mr. Davis, or Dr. Zahler committed inequitable conduct.

CONCLUSION

For the reasons stated above, the Court concludes that (1) Defendant's proposed product infringes claim 8 of the '244 Patent; (2) claim 8 of the '244 Patent is invalid due to obviousness; and (3) claim 8 is not unenforceable due to inequitable conduct; and (4) Plaintiff's Rule 52(c) motion is GRANTED-IN-PART and DENIED-IN-PART. The parties will be directed to submit a proposed order by which the Court may enter final judgment consistent with this Opinion.

An appropriate Order will issue.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BRISTOL-MYERS SQUIBB COMPANY,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 10-805-CJB
	)	
TEVA PHARMACEUTICALS USA, INC.,	)	
	)	
Defendant.	)	

ORDER

At Wilmington, this **11th** day of **February, 2013**:

For the reasons set forth in the Memorandum Opinion issued this date,

IT IS HEREBY ORDERED that

1. Plaintiff Bristol-Myers Squibb Company's ("BMS") verbal Motion for Judgment under Rule 52(c) (*See* D.I. 144 at 744:20–24) is GRANTED-IN-PART and DENIED-IN-PART.

2. Within seven days of the date of this Order, the parties shall jointly submit a proposed form of judgment consistent with the Memorandum Opinion issued this date.

Christopher J. Burke
UNITED STATES MAGISTRATE JUDGE