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.	)	

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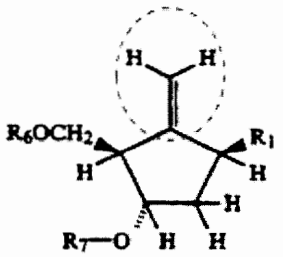
[4] "Heterocyclic" means that the atoms in the compound connect to form a ring shape, and not all of the atoms are carbon. (Tr. 130:20–24) When all of the atoms are carbon, this is called a "carbocyclic ring." (Tr. 40:20-21)

[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)

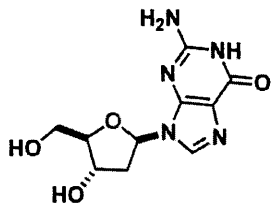


(D.I. 150 at ¶ 2; JTX 1) "Exocyclic" means something that is attached outside of the five-membered ring; an exocyclic methylene group is a carbon-carbon double bond that is attached outside of that ring. (Tr. 210:16-17; 1077:2–18)

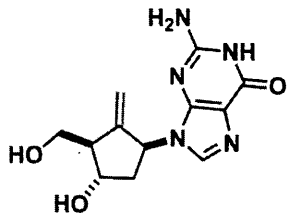
23. The only claim of the '244 Patent asserted in this case is claim 8, which covers the chemical compound entecavir. (D.I. 150 at ¶ 2; 151 at ¶ 3)

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)

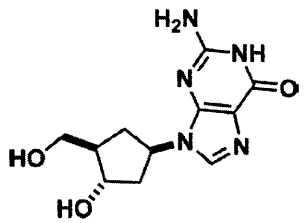
67. An article summarizing the antiviral research to date by Dr. J.A. Montgomery of SRI was published in October 1989 ("Montgomery 1989"). (DTX 172.0003–04) Dr. Montgomery concluded that of the compounds identified by SRI with promising antiviral activity, "[b]y far the most active and selective agents 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.*)

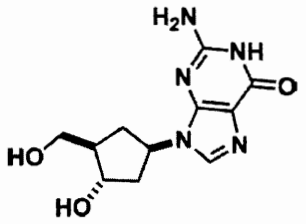
92. Testimony from BMS's own expert, Dr. Bud Tennant, illuminates that the toxicity of 2'-CDG was not well known as of October 1990. Dr. Tennant explained that woodchucks are an animal model used to test potential hepatitis B drugs before they are tested in humans, because the woodchuck hepatitis virus 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)

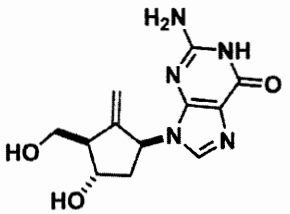
94. Even if some evidence did exist prior to October 1990 indicating that 2'-CDG was associated with toxicity, such evidence was limited, and would not have discouraged the ordinary medicinal chemist from using 2'-CDG as a lead compound. Indeed, Dr. Slusarchyk, the medicinal chemist who designed the 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)