NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SANOFI-AVENTIS U.S. LLC, et al., Plaintiffs, v. FRESENIUS KABI USA, LLC, et al., Defendants.	Civil Action No. 14-7869 (MAS) (LHG) **OPINION** **REDACTED VERSION**

SHIPP, District Judge

This consolidated action[1] arises under the patent laws of the United States. The Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a). The Court conducted an eight-day bench trial on September 18-20 and September 25-29, 2017.[2] The parties submitted

[1] On September 15, 2017, upon consent of the parties, the Court consolidated the following cases for trial: *Sanofi-Aventis U.S., LLC, et al. v. Fresenius Kabi USA, LLC*, 14-7869, 14-8082, 15-2631; *Sanofi-Aventis U.S., LLC, et al. v. Accord Healthcare, Inc.*, 14-8079, 15-2520; *Sanofi-Aventis U.S., LLC, et al. v. Apotex Corp., et al.*, 15-287, 15-1835; *Sanofi-Aventis U.S., LLC, et al. v. Mylan Labs.*, 15-290, 15-3392; and *Sanofi-Aventis U.S., LLC, et al. v. Actavis LLC*, 15-776, 16-3107.

On September 11, 2017, the Court entered the Stipulation to be Bound between Plaintiffs and Defendants Glenmark Pharmaceuticals, Inc., USA and Glenmark Pharmaceuticals Ltd. (15-2523, ECF No. 56.) On September 12, 2017, the Court entered the Stipulation to be Bound between Plaintiffs and Defendants BPI Labs, LLC and Belcher Pharmaceuticals, LLC. (14-8081, ECF No. 58; 15-2521, ECF No. 48.) On September 13, 2017, the Court entered the Stipulation to be Bound between Plaintiffs and Breckenridge Pharmaceutical, Inc. (15-289, ECF No. 79; 15-1836, ECF No. 56.) On September 15, 2017, the Court entered the Stipulation to be Bound between Plaintiffs and Defendants Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (15-2522, ECF No. 48; 16-2259, ECF No. 24.) The Defendants in these cases, therefore, did not participate in the bench trial.

[2] The trial transcript is docketed at ECF numbers 286 through 297.

post-trial briefs on October 31, 2017 and the Court heard closing arguments on November 8, 2017. (ECF No. 284.) The Court has considered the evidence presented at trial and the parties' related arguments and herein sets forth its Findings of Fact and Conclusions of Law pursuant to Federal Rule of Civil Procedure 52(a)(1).[3]

I. BACKGROUND

A. The Parties

Sanofi ("Sanofi") is a corporation organized and existing under the laws of France, having its principal place of business at 54 rue La Boétie, 75008 Paris, France. (SF 1.)[4] Sanofi-Aventis U.S. LLC ("Sanofi U.S.") is an indirectly, wholly-owned U.S. subsidiary of Sanofi and is a company organized and existing under the laws of the State of Delaware, having commercial headquarters at 55 Corporate Drive, Bridgewater, New Jersey 08807. (SF 2.) Aventis Pharma S.A. ("Aventis") is a corporation organized and existing under the laws of France, having its principal place of business at 20 avenue Raymond Aron, 92160 Antony, France. (SF 3.) Rhône-Poulenc Rorer ("RPR") was a predecessor company to Sanofi. (SF 4.)

Fresenius Kabi USA, LLC ("Fresenius") is a corporation organized and existing under the laws of Delaware, with corporate headquarters at Three Corporate Drive, Lake Zurich, Illinois 60047. (SF 6.) Accord Healthcare, Inc. ("Accord") is a corporation organized and existing under

[3] To the extent that any Finding of Fact represents a Conclusion of Law, it is hereby adopted as a Conclusion of Law and vice versa. In evaluating the testimony of the witnesses appearing at trial, and after the Court had the opportunity to hear their testimony and to observe their demeanor, the Court undertook an individualized credibility assessment of each witness and assigned the appropriate weight to the testimony based on the Court's conclusions with respect to credibility. Such determinations are reflected in the Court's factual findings.

[4] The parties stipulated to a number of facts in the Joint Final Pretrial Order. These Stipulated Facts ("SF") required no proof at trial. (Joint Final Pretrial Order, ECF No. 167.) The Court will reference the paragraph number of each Stipulated Fact, not the corresponding page number of the Joint Final Pretrial Order.

the laws of North Carolina, having its principal place of business as 1009 Slater Road, Suite 210B, Durham, North Carolina 27703. (SF 7.) Belcher Pharmaceuticals, LLC is a Florida corporation having a place of business at 6911 Bryan Dairy Road, Suite 210, Largo, Florida 33777. (SF 8.) BPI Labs, LLC ("BPI") is a Florida corporation that has a place of business at 4400 Route 9 South, Suite 1000, Freehold, New Jersey 07728. (SF 9.) BPI is a wholly-owned subsidiary of Belcher Pharmaceuticals, LLC. (*Id.*) Apotex Inc. is a corporation organized and existing under the laws of Canada, with a place of business at 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9. (SF 10.) Apotex Corp. is a corporation organized and existing under the laws of Delaware, with a place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326. (SF 11.)

Breckenridge Pharmaceutical, Inc. ("Breckenridge") is a corporation organized and existing under the laws of Florida with a place of business at 6111 Broken Sound Parkway, NW, Suite 170, Boca Raton, Florida 33487. (SF 12.) Mylan Laboratories Limited ("Mylan") is a corporation organized and existing under the laws of India, having its principal place of business at Opp. IIM, Bilekahalli, Bannerghatta Road, Bangalore, Karnataka 560076, India. (SF 13.) Mylan was formerly known as Onco Therapies Limited. (SF 13.) Actavis LLC ("Actavis") is a Delaware corporation with a place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey 07054. (SF 14.) Actavis was formerly known as Actavis Inc. (SF 14.)

Dr. Reddy's Laboratories, Inc. is a corporation organized and existing under the laws of New Jersey, having its principal place of business at 107 College Road East, Princeton, New Jersey 08540. (SF 15.) Dr. Reddy's Laboratories, Ltd. is a company organized and existing under the laws of India, having its principal place of business at 8-2-337 Road No. 3, Banjara Hills, Hyderabad 500034, India. (SF 16.) Dr. Reddy's Laboratories, Inc. is a subsidiary of Dr. Reddy's Laboratories, Ltd. (SF 16.)

Glenmark Pharmaceutical Inc., USA is a Delaware corporation, having its principal place of business at 750 Corporate Drive, Mahwah, New Jersey 07430. (SF 17.) Glenmark Pharmaceuticals Inc., USA was formerly known as Glenmark Generics, Inc., USA, and is the North American Division of Glenmark Pharmaceuticals Ltd. (SF 17.) Glenmark Pharmaceuticals Ltd. is a company organized and existing under the laws of India, having its principal place of business at Glenmark House, B D S Marg, Chakala, Off Western Express Highway, Andheri (East), Membai 400099, Maharashtra, India. (SF 18.)

B. The '170 Patent

United States Patent No. 5,847,170 ("the '170 patent") is entitled "Taxoids, Their Preparation And Pharmaceutical Compositions Containing Them." (SF 19.) Hervé Bouchard, Jean-Dominique Bourzat, and Alain Commerçon are listed as the named inventors of the '170 patent. (SF 20.) The '170 patent issued from U.S. Patent Application Serial No. 08/622,011, filed on March 26, 1996, and claims priority from U.S. Provisional Application No. 60/010,144, filed January 17, 1996; French Application No. 9503545, filed March 27, 1995; and French Application No. 9515381, filed December 22, 1995. (SF 21.) On December 8, 1998, the United States Patent and Trademark Office issued the '170 patent. (SF 22.) When it issued in 1998, the '170 patent was assigned to RPR. (SF 23.) The '170 patent is now assigned to Aventis Pharma S.A. (SF 24.) The priority date for Claims 1-2 of the '170 patent is March 27, 1995 and the effective U.S. filing date for these claims is January 17, 1996. (SF 24.) The '170 patent is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") for JEVTANA® (hereinafter JEVTANA® or "Jevtana") (NDA No. 201023). (SF 25.) The '170 patent expires on March 6, 2021, and the Orange Book states that it has a period of pediatric exclusivity until September 26, 2021. (SF 26.)

C. The '592 Patent

United States Patent No. 8,927,592 ("the '592 patent") is entitled "Antitumoral Use Of Cabazitaxel." (SF 27.) Sunil Gupta is the named inventor of the '592 patent. (SF 28.) The '592 patent issued from U.S. Patent Application Number 13/456,720 ("the '720 application"), filed April 26, 2012, and the '720 application is a continuation of International Application No. PCT/IB2010/054866, filed October 27, 2010. (SF 29-30.) International Application No. PCT/IB2010/054866 claims priority to seven U.S. provisional patent applications: Provisional Application No. 61/256,160, filed October 29, 2009; Provisional Application No. 61/293,903, filed January 11, 2010; Provisional Application No. 61/355,834, filed June 17, 2010; Provisional Application No. 61/355,888, filed June 17, 2010; Provisional Application No. 61/369,929, filed August 2, 2010; Provisional Application No. 61/383,933, filed September 17, 2010; and Provisional Application No. 61/389,969, filed October 5, 2010. (SF 31.)

The priority date for Claims 10, 14-16, 21, 26, and 30 of the '592 patent is October 29, 2009. (SF 32.) The effective U.S. filing date for these claims is October 29, 2009. (SF 32.) The priority date and effective filing date for Claim 11 of the '592 patent is January 11, 2010. (SF 33.) The priority date and effective U.S. filing date for Claims 7 and 8 of the '592 patent is June 17, 2010. (SF 34.) The '592 patent is owned by Aventis and issued on January 6, 2015. (SF 35-36.) The '592 patent is listed in the Orange Book for Jevtana (NDA No. 201023). (SF 37.) The '592 patent expires on October 27, 2030, and the Orange Book states that it has a period of pediatric exclusivity until April 27, 2031. (SF 38.)

D. Sanofi's JEVTANA® Product

Sanofi U.S. holds approved New Drug Application ("NDA") No. 201023 for cabazitaxel injection, 60 mg/1.5 mL (40 mg/mL), which is prescribed and sold in the United States under the

trademark JEVTANA®. (SF 39.) The United States Food and Drug Administration ("FDA") approved NDA No. 201023 on June 17, 2010. (SF 39.)

E. Defendants' Proposed Products

Defendants' proposed products are set forth in the chart below.[5]

Application with FDA	Proposed Product	Date of Notice Letter	Patent Challenged	Basis for Certification filed with FDA
Fresenius				
B2 NDA No. 207937	Cabazitaxel Injection, 60 mg/3 mL solution (20 mg/mL)	Nov. 3, 2014	'170 patent	Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, or sale of Fresenius's proposed product. (SF 44.)
B2 NDA No. 207937	Cabazitaxel Injection, 60 mg/3 mL solution (20 mg/mL)	Apr. 2, 2015	'592 patent	Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, and/or sale of Fresenius's proposed product. (SF 46.)
ANDA No. 207591	Cabazitaxel Injection, 60 mg/1.5 mL	Nov. 18, 2014	'170 patent	Certification pursuant to 21 U.S.C. § 355 (j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, or sale of Fresenius's proposed ANDA product. (SF 51.)
ANDA No. 207591	Cabazitaxel Injection, 60 mg/1.5 mL	Apr. 2, 2015	'592 patent	Certification pursuant to 21 U.S.C. § 355 (j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, or sale of Fresenius's Proposed ANDA Product. (SF 53.)

[5] All of the submissions to the FDA include reference to Sanofi U.S.'s NDA No. 201023. In addition, every proposed product sought approval for use in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

Application with FDA	Proposed Product	Date of Notice Letter	Patent Challenged	Basis for Certification filed with FDA
Accord				
B2 NDA No. 207949	Cabazitaxel Injection, 20 mg/mL, 3 mL (SF 54.)	Nov. 25, 2014	'170 patent	Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Accord's Proposed B2 NDA Product. (SF 58.)
B2 NDA No. 207949	Cabazitaxel Injection, 20 mg/mL, 3 mL (SF 54.)	Mar. 11, 2015	'592 patent	Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Accord's Proposed B2 NDA Product. (SF 60.) On June 25, 2015, Accord received tentative approval from the FDA for the Accord B2 NDA. (SF 61.)
ANDA No. 207693	Cabazitaxel Injection, 60 mg/1.5 mL (SF 62)	Nov. 24, 2014	'170 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Accord's Proposed ANDA Product. (SF 66.)
ANDA No. 207693	Cabazitaxel Injection, 60 mg/1.5 mL (SF 62)	Mar. 11, 2015	'592 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Accords' Proposed ANDA Product. (SF 68.) On October 24, 2016, Accord received tentative approval from the FDA for the Accord ANDA. (SF 69.)
BPI				
ANDA No. 207735	Cabazitaxel 60 mg/1.5 mL solution for	Nov. 19, 2014	'170 patent	Certification pursuant to 23 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale,

Application with FDA	Proposed Product	Date of Notice Letter	Patent Challenged	Basis for Certification filed with FDA
	intravenous infusion (SF 70.)			and/or importation of BPI's Proposed ANDA Product. (SF 74.)
ANDA No. 207735	Cabazitaxel 60 mg/1.5 mL solution for intravenous infusion (SF 70.)	Dec. 9, 2014	'170 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of BPI's Proposed ANDA Product. (SF 76.)
ANDA No. 207735	Cabazitaxel 60 mg/1.5 mL solution for intravenous infusion (SF 70.)	Mar. 12, 2015	'592 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of BPI's Proposed ANDA Product. (SF 78.)
Apotex				
ANDA No. 207736	Cabazitaxel injection, 60 mg/1.5 mL (SF 79.)	Dec. 4, 2014	'170 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's Proposed ANDA Product. (SF 83.)
ANDA No. 207736	Cabazitaxel injection, 60 mg/1.5 mL (SF 79.)	Jan. 28, 2015	'592 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's Proposed ANDA Product. (SF 85.) On January 26, 2017, Apotex received tentative approval from the FDA for the Apotex ANDA. (SF 86.)
Breckenridge				
ANDA No. 207619	Cabazitaxel solution, IV, 60 mg/1.5 mL (40	Dec. 2, 2014	'170 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale,

Application with FDA	Proposed Product	Date of Notice Letter	Patent Challenged	Basis for Certification filed with FDA
	mg/mL) (SF 87.)			and/or importation of Breckenridge's Proposed ANDA Product. (SF 91.)
ANDA No. 207619	Cabazitaxel solution, IV, 60 mg/1.5 mL (40 mg/mL) (SF 87.)	Jan. 26, 2015	'592 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Breckenridge's Proposed ANDA Product. (SF 93.)
Mylan				
ANDA No. 207381	Cabazitaxel injection [60 mg/1.5 mL] [40 mg/mL] (SF 94.)	Dec. 4, 2014	'170 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, and/or sale of Mylan's Proposed ANDA Product. (SF 98.)
ANDA No. 207381	Cabazitaxel injection [60 mg/1.5 mL] [40 mg/mL] (SF 94.)	May 5, 2015	'592 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, and/or sale of Mylan's Proposed ANDA Product. (SF 100.)
Actavis				
ANDA No. 207970	Cabazitaxel Injection, 10 mg/mL. (SF 101.)	Dec. 22, 2014	'170 patent	Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, or sale of Actavis's Proposed B2 NDA Product. (SF 105.)
ANDA No. 207970	Cabazitaxel Injection, 10 mg/mL. (SF 101.)	Apr. 23, 2015	'592 patent	Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, or sale of Actavis's Proposed B2 NDA Product. (SF 107.) Actavis received tentative approval from the FDA for the Actavis B2 NDA. (SF 108.)

Application with FDA	Proposed Product	Date of Notice Letter	Patent Challenged	Basis for Certification filed with FDA
DRL				
ANDA No. 207718	Cabazitaxel, 60 mg/1.5 mL. (SF 109.)	Mar. 18, 2015	'592 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of DRL's Proposed ANDA Product. (SF 113.)
ANDA No. 207718	Cabazitaxel, 60 mg/1.5 mL. (SF 109.)	Mar. 10, 2016	'170 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of DRL's Proposed ANDA Product. (SF 115.)
Glenmark				
ANDA No. 207784	60 mg/1.5 mL (40 mg/mL) cabazitaxel for injection. (SF 116.)	Mar. 27, 2015	'592 patent	Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Glenmark's Proposed ANDA Product. (SF 120.)

F. **Defendants' Proposed Product Labels**

Product	Label Comparison
Fresenius's Proposed ANDA Product	*See* FCAB00345193-235. (SF 121.)
Fresenius's Proposed B2 NDA Product	*See* FCAB00011220-260. (SF 124.)
Accord's Proposed ANDA Product	Except for the corporate identity and product information, the product label for Accord's Proposed ANDA Product is identical to the label for Sanofi's JEVTANA® product. (SF 127.)
Accord's Proposed B2 NDA Product	Except for the corporate identity, product information, inactive ingredients, and number of dilutions, the product label for Accord's Proposed B2 NDA Product is identical to the label for Sanofi's JEVTANA® product. (SF 130.)

Product	Label Comparison
BPI's Proposed ANDA Product	Except for the corporate identity and product information, the product label for BPI's Proposed ANDA Product is identical to the label for Sanofi's JEVTANA® product. (SF 133.)
Apotex's Proposed ANDA Product	*See* AAPO-CAB00013976-4027. (SF 135.)
Breckenridge's Proposed ANDA Product	*See* at BRKCAB-00088842-889. (SF 137.)
Mylan's Proposed ANDA Product	*See* MYL_CAB0000039-094. (SF 139.)
Actavis's Proposed B2 NDA Product Prescribing and Patient Information	*See* ACT_CABAZ_00012190-225. (SF 141.)
DRL's Proposed ANDA Product	Except for the corporate identity, product information, and inactive ingredients, the product label for DRL's Proposed ANDA Product is identical to the label for Sanofi's JEVTANA® product. (SF 144.)
Glenmark's Proposed ANDA Product	Except for the corporate identity and product information, the product label for Glenmark's Proposed ANDA Product is identical to the label for Sanofi's JEVTANA® product. (SF 147.)

II. LEGAL STANDARDS

Plaintiffs must prove infringement by a preponderance of the evidence. *See Medtronic, Inc. v. Mirowski Family Ventures, LLC*, 134 S. Ct. 843, 846 (2014); *Integrated Tech. Corp. v. Rudolph Techs., Inc.*, 734 F.3d 1352, 1356 (Fed. Cir. 2013); *Siemens Med. Sols. USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1279, 1283 (Fed. Cir. 2011); *Mannesmann Demag Corp. v. Engineered Metal Prods. Co.*, 793 F.2d 1279, 1282 (Fed. Cir. 1986); *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984); *Curlin Med. Inc. v. Acta Med., LLC*, 228 F. Supp. 3d 355, 358 (D.N.J. 2017) (citing *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008)).

Defendants must prove invalidity by clear and convincing evidence. *See* 35 U.S.C. § 282 ("The burden of establishing invalidity of a patent or any claim thereof shall rest on the party

asserting such invalidity."); *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 102 (2011); *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) (quoting *PharmaStem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007)); *Tech. Licensing Corp.*, 545 F.3d at 1327; *Purdue Pharm. Prods. L.P. v. Actavis Elizabeth LLC*, No. 12-5311, 2015 WL 5032650, at *10 (D.N.J. Aug. 25, 2015) (quoting *Linear Tech Corp. v. Int'l Trade Comm'n*, 566 F.3d 1049, 1066 (Fed. Cir. 2009)). Obviousness must be considered against the totality of the prior art. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014). In making an obviousness determination, courts must consider secondary considerations or objective indicia of non-obviousness. *See id.* "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007); *see also Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1341 (Fed. Cir. 2015). "Thus, a defendant asserting obviousness in view of a combination of references has the burden to show by clear and convincing evidence that a person of ordinary skill in the [art] . . . had reason to combine the elements in the manner claimed." *Senju Pharm. Co.*, 780 F.3d at 1341 (citing *KSR Int'l Co.*, 550 U.S. at 418-19). Additionally, "a defendant must also demonstrate that a person of ordinary skill in the art [("POSA")] would have [had] a reasonable expectation of success in combining the elements." *Id.* (citing *PharmaStem Therapeutics, Inc.*, 491 F.3d at 1360).

Furthermore, in making an obviousness determination, courts must avoid hindsight analysis. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070-71 (Fed. Cir. 2012) (holding that courts should reject "hindsight claims of obviousness" where "a defendant urges an obviousness finding by merely throwing metaphorical darts at a board in hopes of arriving at a successful result, but the prior art gave either no indication

of which parameters were critical or no direction as to which of many possible choices is likely to be successful." (internal quotations omitted) (quoting *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009))); *see also Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (hindsight is "always inappropriate for an obviousness test").

The longstanding prohibition of the doctrine of obviousness-type double patenting "prohibits an inventor from extending his right to exclude through claims in a later-expiring patent that are not patentably distinct from the claims of the inventor's earlier-expiring patent." *Gilead Scis., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1210 (Fed. Cir. 2014); *see, e.g., Singer Mfg. Co. v. June Mfg. Co.*, 163 U.S. 169, 185 (1896) ("It is self-evident that on the expiration of a patent the monopoly created by it ceases to exist, and the right to make the thing formerly covered by the patent becomes public property. It is upon this condition that the patent is granted."); *Miller v. Eagle Mfg. Co.*, 151 U.S. 186, 197-98 (1894); *Suffolk Co. v. Hayden*, 70 U.S. 315, 317 (1865); *Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1346 (Fed. Cir. 2010); *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985). The obviousness-type double patenting analysis involves a two-step process. First, the Court "construes the claims in the earlier patent and the claims in the later patent and determines the differences." *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1374 (Fed. Cir. 2014) (internal quotations and citations omitted). Second, the Court "determines whether those differences render the claims patentably distinct. A later claim that is not patentably distinct from, *i.e.*, is obvious over or anticipated by, an earlier claim is invalid for obviousness-type double patenting." *Id.* (internal quotations and citations omitted).

III. '170 PATENT

A. Invention Story

Around 1989, Sanofi launched a medicinal chemistry program to search for taxane analogs to treat cancers. (Tr. (Bouchard) 1017:4-6; Tr. (Vrignaud) 1108:10-20.) The program used existing taxanes, docetaxel, which was then under development by Sanofi, and paclitaxel, as reference compounds. (Tr. (Bouchard) 1018:5-8; Tr. (Vrignaud) 1113:6-14.) The program's goal was to identify taxane analogs that worked at least as well as docetaxel in sensitive tumors, but had greater activity than docetaxel in resistant tumors, and to improve water solubility. (Tr. (Vrignaud) 1108:14-20; Tr. (Bouchard) 1035:13-20.)

Over the next seven years, Sanofi researchers, including Dr. Hervé Bouchard, explored "almost every part" of the taxane structure, including modifications to the side chain and modifications to the core at C-2, C-4, C-5, C-6, C-7, C-9 and C-10. (Tr. (Bouchard) 1027:3-23; Tr. (Vrignaud) 1109:4-9.) The modifications varied, and included the addition of different functional groups and changes in the stereochemistry of different portions of the molecule. (*Id.* at 1027:3-1029:6; *see generally* JTX-133; JTX-153; JTX-154; JTX-155.) Certain compounds were synthesized in a matter of days and others compounds took months to successfully produce. (Tr. (Bouchard) 1027:24-1028:5.)

Once Sanofi had successfully synthesized a novel compound, it was evaluated in a series of *in vitro* and *in vivo* tests to determine the biological properties of the compound. (Tr. (Bouchard) 1019:1-1020:16; Tr. (Vrignaud) 1109:10-24.) First, an *in vitro* tubulin assay was used to confirm that the newly synthesized compound was still acting as a taxane, *i.e.*, binding to the tubulin target. (Tr. (Bouchard) 1019:7-17; Tr. (Vrignaud) 1109:10-1110:14, 1112:9-12; *see also* Tr. (Roush) 1348:4-1349:12.) Second, *in vitro* cellular assays were used to assess a compound's potency in

sensitive and resistant cell lines. (Tr. (Bouchard) 1019:25-1020:11; Tr. (Vrignaud) 1109:10-24, 1115:22-1117:22, 1120:16-1121:1.) These tests compared the novel compounds head-to-head to docetaxel in each cell line. (Tr. (Vrignaud) 1117:17-1118:8, 1121:2-16; *see also* Tr. (Roush) 1280:19-24.) Third, the *in vivo* activity of the new compounds was then assessed in an animal model using mice bearing tumors treated with docetaxel. (Tr. (Bouchard) 1020:12-16; Tr. (Vrignaud) 1125:6-1126:17.)

Sanofi researchers, including the three inventors of the '170 patent, would review the data from the *in vitro* and *in vivo* tests and "decide[] which new compounds should be made afterwards." (Tr. (Bouchard) 1020:17-23.) The *in vitro* and *in vivo* tests each had inherent limitations. (Tr. (Bouchard) 1019:18-24; Tr. (Vrignaud) 1115:8-21, 1119:6-1120:15.) Initial attempts to modify the C-7 and C-10 positions were unsuccessful. (JTX-153 at 186, 188; Tr. (Bouchard) 1043:1-1047:15.) In January 1994, Sanofi scientists discovered that replacement of the C-7 hydroxy with a C-7, 8, 19 cyclopropane structure led to improvements *in vitro* and *in vivo* in docetaxel-resistant tumors. (Tr. (Bouchard) 1040:13-1041:11.) This led to the discovery of larotaxel, which was chosen as the lead candidate for further development. (JTX-133 at SA_JEV_0182637; Tr. (Bouchard) 1040:13-1041:11; Tr. (Vrignaud) 1152:20-1153:8, 1203:6-8.) Dr. Bouchard testified that he made more than 450 compounds as part of the tax analog project and, out of those, only larotaxel and cabazitaxel entered into human studies. (Tr. (Bouchard) 1020:24-1021:1.)

In April 1994, a derivative of docetaxel was synthesized at RPR with a single C-10 methoxy group: RPR 112698. (JTX-133 at SA_JEV_0182655; Tr. (Bouchard) 1036:14-1037:14, 1050:18-1051:2, 1100:2-18.) Dr. Bouchard also added back the acetoxy group removed when modifying paclitaxel to docetaxel onto the C-10 of docetaxel, forming 10-acetoxy docetaxel. (JTX-133 at

SA_JEV_0182586; Tr. (Bouchard) 1035:7-14.) Dr. Bouchard found that this new compound had good *in vitro* and *in vivo* activity. (*Id.*) On November 15, 1994, Dr. Bouchard synthesized cabazitaxel, the C-7, C-10 di-methyoxy derivative, for the first time. (JTX-154 at 96; Tr. (Bouchard) 1054:2-25, 1057:19-1058:8.)

B. Infringement

Defendants concede that their products infringe Claims 1 and 2 of the '170 patent. (Infringement Stipulation, ECF No. 242.) Accordingly, the Court will consider whether the patent is invalid.

C. Invalidity

1. POSA

Plaintiffs assert that a POSA "in March 1995 would have been someone with a Ph.D. in organic chemistry, medicinal chemistry, or a closely related discipline and at least two years of experience synthesizing or characterizing drug molecules. Alternatively, a POSA could have had a bachelor's degree or master's degree in organic chemistry, medicinal chemistry, or a closely related discipline with a greater amount of experience synthesizing or characterizing drug molecules." (Tr. (Roush) 1242:21-1244:12.) Defendants assert that a POSA for the '170 patent would have had a high level of education, such as having at least a master's degree, but more likely a Ph.D. in organic chemistry, medicinal chemistry, or a related discipline, and experience in the design and synthesis of drug molecules. (Tr. (Kingston) 106:3-13; Tr. (Heathcock) 822:14-23.) Alternatively, a POSA could have had a lower level of formal education if such a person had a greater amount of experience. (Tr. (Heathcock) 822:23-823:9.) Here, the parties essentially agree on the skills of a POSA. Moreover, the experts all testified that their opinions would be the same even if the Court adopted the opposing party's definition of a POSA. The Court finds the proposed

POSA definitions substantially similar and the differences inconsequential and declines to adopt either definition.

2. Testimony[6]

a. Herve Bouchard, Ph.D.[7]

Dr. Bouchard is a medicinal chemist at Sanofi and the lead inventor on the '170 patent. (Tr. (Bouchard) 1016:4-8, 1017:14-24.) Dr. Bouchard was responsible for the group of medicinal chemists within the taxane analogue group at RPR, a predecessor to Sanofi, and personally synthesized cabazitaxel for the first time on November 15, 1994. (*Id.* at 1016:18-23, 1021:6-11, 1057:13-1058:17.)

b. Clayton R. Heathcock, Ph.D.[8]

Dr. Heathcock testified that "because docetaxel had been superior in all of the kinds of comparisons that had been made, I think a person of skill would certainly consider that the best starting point" for a lead compound. (Tr. (Heathcock) 843:3-6.) According to Dr. Heathcock, the docetaxel side chain gave better results than paclitaxel and "you got a better compound if you didn't have the acetoxy group at C-10." (*Id.* at 843:22-25.)

Dr. Heathcock testified that Claims 1 and 2 of the '170 patent would have been obvious to a POSA in light of the prior art compound docetaxel and the knowledge that was available in the art at the time. (*Id.* at 819:2-6.) Dr. Heathcock's testimony largely centered on P-Glycoprotein

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[6] The Court will not set forth testimony in detail in this section. In addition, certain testimony may be reflected in the Prior Art and other sections of this Opinion.

[7] Details with respect to Dr. Bouchard's research are set forth in the Invention Story at III.A, *supra*.

[8] Dr. Heathcock was accepted by the Court as an expert in medicinal chemistry and chemical synthesis. (Tr. 816:7-817:2.)

("Pgp"), including how Pgp works to cause multidrug resistance, the reasons why a POSA would focus on Pgp as the mechanism of resistance, and the strategic modifications a POSA would be motivated to make to docetaxel to address the Pgp issues. (*Id.* at 858:19-897:19.) Dr. Heathcock testified that it was known that Pgp affected both paclitaxel and docetaxel, the prior art suggested the approaches of improving cell permeability or reducing the Pgp affinity to overcome the problem of Pgp, and that a POSA "would be led to the conclusion that changing the hydroxyl groups at [C-]7 and [C-]10 to methoxy groups would be expected to accomplish both of these goals." (*Id.* at 897:16-19.)

c. David G.I. Kingston, Ph.D.[9]

Dr. Kingston testified on behalf of Defendants that a POSA would choose docetaxel as a lead compound for further development. Dr. Kingston testified that the data in Ringel, Riou, Bissery and Verweij all lent support for the proposition that a POSA would choose docetaxel. (Tr. (Kingston) 147:23-148:1.)

Dr. Kingston also testified that Claims 1 and 2 of the '170 patent would be obvious to a POSA based on the prior art. (*Id.* at 99:11-13; 187:21-25.) Specifically, Dr. Kingston opined that Claim 1 of the '170 patent is obvious in light of Wong, Golik, and Kant. (*Id.* at 186:12-13.) Dr. Kingston testified that Claim 2 was "gobbledygook," "[f]ull of sound and fury, signifying nothing" because a POSA would have a reasonable expectation of success using taxane formulations for cabazitaxel. (*Id.* at 187:1-15.) According to Dr. Kingston, the hydroxyl groups are chemically the easiest to modify and, of the four OH groups, the hydroxyl groups at the C-7 and C-10 positions could be modified readily by known chemistry. (*Id.* at 153:18-22.) Dr. Kingston testified that the

[9] Dr. Kingston was accepted by the Court as an expert in taxane chemistry, organic chemistry, and taxane synthesis. (Tr. (Kingston) 105:6-9.)

C-2' position on the side chain was not a good candidate compared to the other hydroxyl groups because the body of work by 1995 showed that changes to that hydroxyl group resulted in loss of activity. (*Id.* at 152:18-153:1.) In addition, Dr. Kingston testified that the C-1 position was not a good candidate because it is in a very difficult position to change. (*Id.* at 153:5-16.) Dr. Kingston further testified that a POSA would be interested in maintaining the entire structure of docetaxel with small modifications at the C-7 and C-10 positions. (*Id.* at 155:7-9.)

Dr. Kingston testified that a POSA would combine the teachings and make changes at both C-7 and C-10 based on "the additivity principle," "a well-known principle of medicinal chemistry." (*Id.* at 179:13-19.) Dr. Kingston also testified that a POSA would have a reasonable expectation of success that making the change to C-7 and C-10 would result in an improved compound. (*Id.* at 179:20-24.)

d. Richard Ludueña, Ph.D.

Defendants offered the videotaped deposition testimony of Plaintiffs' expert, Dr. Ludueña. Dr. Ludueña testified that he did not have any opinion as to whether docetaxel would have been a good starting point for taxane development by 1995. (DTX-2724 (Ludueña) at Clip 29.) Dr. Ludueña testified that a POSA in 1995 would have viewed docetaxel as a promising compound, but with some issues related to activity in resistant cells. (*Id.* at Clip 30.) Dr. Ludueña also testified that someone working in the field of developing docetaxel analogues in 1995 would be interested in improving the performance of those analogues against drug-resistant cells (*id.* at Clips 34-35).

In addition, Dr. Ludueña testified that he does not consider himself an expert in Pgp. (*Id.* at Clip 72.) Nevertheless, he testified regarding mechanisms of resistance and noted that, as of 1995, Pgp was known and an object of interest. (*Id.* at Clip 69.) Dr. Ludueña, however, disagreed

with the proposition that, as of 1995, Pgp was the most well-known mechanism of drug resistance for chemotherapy agents. (*Id.* at Clip 68.) Dr. Ludueña also acknowledged that abstracts from the American Society of Clinical Oncology's 30th annual meeting in May 1994 provides some evidence that Pgp-mediated resistance was relevant to clinically observed Taxol resistance. (*Id.* at Clips 107-08.)

e. Professor Iwao Ojima

Defendants offered the videotaped deposition testimony of Plaintiffs' expert, Dr. Ojima. The excerpts included testimony regarding a number of prior art references, including: Wils; Ojima 1994; Hait; Kant, Klein, Golik, Wong, Ford and Hait.[10]

f. Dr. Roush[11]

With respect to the selection of a lead compound, Dr. Roush, Plaintiffs' expert, testified that he did not agree that a POSA would only select docetaxel as the lead compound because a POSA would have looked to the FDA-approved drug, which was paclitaxel. (Tr. (Roush) 1282:8-19.) In addition, Dr. Roush testified that Dr. Kingston and other laboratories were using paclitaxel as a lead compound in March 1995. (*Id.* at 1286:8-1288:10.) Dr. Roush, nevertheless, acknowledged that there were prior art paper publications that showed that docetaxel was more potent in a variety of cell lines. (*Id.* at 1284:15-17.)

With respect to simultaneous changes to multiple sites, Dr. Roush testified that "a [POSA] doesn't go off and start making changes to multiple sites simultaneously." (*Id.* at 1258:9-11.) He noted that Dr. Bouchard, the inventor of the '170 patent, was not "just looking at one place at a

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[10] Dr. Ojima's testimony is reflected in the Prior Art section *infra*.

[11] Dr. Roush was accepted by the Court as an expert in medicinal chemistry and organic chemistry. (Tr. 1241:21-25.)

time and then moving to a different place. He's looking at the entire molecule in a contemporaneous manner, but with each series of experiments it's one change at a time." (*Id.* at 1258:23-1259:2.) As to the different positions that could be modified on taxanes, Dr. Roush testified that virtually every position on the paclitaxel molecule was being modified in the relevant time period. (*Id.* at 1290:21-1291:2.) Dr. Roush testified that the prior art was not focused on the C-7 and C-10 positions. (*Id.* at 1295:22-25.) Dr. Roush further testified that modifications were being attempted at the C-1, C-2, C-4, C-5, C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-2', and C-3' positions. (*Id.* at 1290:22-1294:23.) In addition, Dr. Roush testified that "integrating over all the various prior publications, . . . at least a thousand" taxane compounds were discussed as of March 1995. (*Id.* at 1295:16-21.)

g. Patricia Vrignaud, Ph.D.[12]

Dr. Vrignaud, a former Sanofi employee, was involved in the preclinical screening program for cabazitaxel and RPR's other docetaxel analogues. (Tr. (Vrignaud) 1105:5-1108:20.) Dr. Vrignaud helped prepare the cabazitaxel preclinical dossier for submission to the FDA during the cabazitaxel approval process. (*Id.* at 1153:9-14.)

3. Prior Art

The prior art to the '170 patent includes:

a. The '470 Patent

U.S. Patent No. 4,814,470 ("the '470 patent") was issued on March 21, 1989 and was assigned to RPR, a predecessor to Sanofi. This patent discloses the structure and synthesis of

[12] Details with respect to Dr. Vrignaud's role in the research process are set forth in the Invention Story at III.A, *supra*.

docetaxel from 10-DAB and the anticancer activity of docetaxel. (Tr. (Heathcock) 829:11-831:8; JTX-119, '470 patent (CabRef0001534-44).)

b. *Taxane Anticancer Agents* (Georg) (JTX-162)

Taxane Anticancer Agents, published in December 1994, contains chapters summarizing some of the key lectures from the March 1994 ACS taxane symposium. The book, co-edited by Dr. Ojima, was referred to as the "taxane bible" because it presented the key work in the taxane field at the time. (Tr. (Heathcock) 833:10-23, 849:21-850:4, 910:10-911:4; Tr. (Bouchard) 1077:3-16, 1078:21-1079:5; Tr. (Roush) 1286:23-1287:11, 1288:18-1289:19; DTX-2725 (Ojima) at Clips 101-02; JTX-162/DTX-2196I Georg, ix (CabRef0000820).)

c. Bissery (JTX 32)

The Bissery article ("Bissery") is entitled *Experimental Antitumor Activity of Taxotere, a Taxol Analogue*. (JTX-32.) Dr. Kingston testified that from the Bissery article, a POSA would conclude that docetaxel would be the better compound to start with over paclitaxel because the two doses of Taxotere that were evaluated resulted in longer life extensions for the treated animals. (Tr. (Kingston) 141:18-142:9.)

d. Commerçon (JTX-109)

Commerçon is a chapter in *Taxane Anticancer Agents* (Georg) which was authored by RPR scientists and provides a summary of taxane structure activity relationships ("SAR"). Specifically, Commerçon discloses the potency impact of making changes at certain positions on the taxane core. (Tr. (Heathcock) 849:21-852:21; JTX-109 at 235 (CabRef0000200).) Dr. Bouchard testified that the contents of Commerçon reflected the state of RPR's taxane work as of March 1994. (Tr. (Bouchard) 1097:11-1099:5).

e. **EP '910** (JTX-125)

EP '910 is a European patent application assigned to BMS. It was published in 1994 and discloses: (1) the efficacy of paclitaxel and docetaxel to treat cancer; and (2) that increasing the lipophilicity of the C-7 hydroxy position of the taxane core could improve the potency of the compound in treating resistant cancer cells. (Tr. (Heathcock) 893:6-896:19; JTX-125, EP '910 (CabRef0000215-310).)

f. **Golik** (JTX-111)

The Golik patent ("Golik" or "the '577 patent") is entitled "Phosphonooxymethyl or methylbiomethys ethers of taxane derivatives as antitumor agents." (JTX-111.) The Golik researchers were chemists from Bristol-Myers Squibb (JTX-111 at Cover) looking to discover more water-soluble taxanes (JTX-111 at 2:42-51; JTX-125 at 2:36-49). The Golik researchers provided *in vitro* data for four compounds: Examples 1, 3, 4, and 1(a). (JTX-111 at 22:1-17; JTX-125 at 17:16-50.) The 7-O methylthiomethyl derivative of docetaxel is referred to as compound Example 1(a). (Tr. (Kingston) 166:8-16; JTX-111 at 22 (CabRef0000332)). Example 1(a) was more potent than docetaxel and paclitaxel in a single resistant cell line. (Tr. (Heathcock) 895:18-896:1; Tr. (Roush) 1363:20-1364:19; JTX-125 17:49-50.) Page 22 of Golik discloses biological testing data of certain taxane derivatives. (JTX 111 at 22 (CabRef0000332); Tr. (Kingston) 166:5-7). This data compares the effect of paclitaxel, docetaxel, and Example 1(a) on normal and resistant cell lines. (Tr. (Kingston) 166:8-22.)

Golik teaches that both paclitaxel and docetaxel have effective antitumor activity in *in vivo* animal models. Specifically, Golik teaches that "a semi-synthetic analogue of paclitaxel named Taxotere® has also been found to have good antitumor activity in animal models" and "is also currently undergoing clinical trials in Europe and the United States." (JTX-111, Golik at 2

(CabRef0000312).) Dr. Ludueña testified that Golik shows that, prior to 1995, Bristol-Myers Squibb had been studying the effects of modification on a group of cell lines thought to be resistant. (DTX-2724 (Ludueña) at Clips 164-65.) Furthermore, Dr. Ludueña testified that modification of the C-7 position of the taxane increased the cytotoxicity of the compound in Golik. (*Id.* at Clip 175.)

g. Greene (JTX-128)

Greene was published in 1991 and is a well-known and widely-used reference in the chemical arts that provides methods for performing many types of chemical reactions. The chemical methods disclosed by Greene are derived from examples in the contemporary scientific literature. (Tr. (Heathcock) 928:16-929:5; Tr. (Bouchard) 1066:22-1067:5.) Greene stated that ethers are the most used protective groups in organic synthesis and noted that ethers "are formed and removed under a wide variety of conditions." (JTX-128 at 14 (CabRef0012735).) Greene discloses eleven different procedures for converting a hydroxy group into a methoxy group. (Tr. (Heathcock) 928:24-931:11; JTX-128 at 15-16 (CabRef0012735-37).) Dr. Heathcock testified that Item 11 ["MeI or Me_2SO_4,[13] NaH or KH, THF] represents Greene's "standard method for introducing the methyl ether function on to hindered and unhindered alcohols." (Tr. (Heathcock) 929:14-930:3; JTX-128 at 16 (CabRef00127-37).) Dr. Heathcock further testified that a medicinal chemist would consider the hydroxyl groups at C-7 and C-10 in docetaxel to be unhindered alcohols. (*Id.* at 930:15-21.)

h. Hait (JTX-102)

The Hait paper ("Hait"), published in 1992, provides a "hypothetical drug binding site on Pgp based on analogies with the binding of antipsychotic drugs to calmodulin." (JTX-102 at 104 (Fig. 2.)) According to Dr. Heathcock, Hait teaches that good substrates for Pgp would have both

a more hydrophobic region and a more hydrophilic region. (Tr. (Heathcock) 882:20-888:19; JTX-102 at 103-107 (CabRef0001259-63)). Hait's hypothetical binding model relates to inhibitors, also called "chemosensitizers." (JTX-102 at 104 (Fig. 2); Tr. (Roush) 1332:12-1333:8; Tr. (Heathcock) 973:10-25.) Inhibitors are compounds which shut down pumping activity but are not themselves pumped out of cells. (Tr. (Roush) 1332:12-1333:25.) Dr. Ludueña testified that nothing from Hait suggests that the binding interactions between phenothiazine and Pgp reflect or would be similar to the binding interactions between a taxane and Pgp. (DTX-2724 (Ludueña) at Clips 202-03.)

i. **Kant** (JTX-114)

The Kant paper ("Kant"), entitled "A Chemoselective Approach to Functionalize the C-10 Position of 10-Deacetylbaccatin III Synthesis and Biological Properties of Novel C-10 Taxol Analogues," describes work by taxane researchers at Bristol-Myers Squibb. (JTX-114 at 5543.) Kant was published in 1994 and studied the effect of replacing the C-10 group of paclitaxel with other substituents including a methoxy group. (JTX-114 at 5545 (CabRef0001266).) Kant also taught that the preferred way to synthesize high-yielding taxane analogues was to start with 10-DAB. Kant was considered by the U.S. Patent and Trademark Office ("PTO") while the '170 patent was pending. (JTX-1 at Cover; Tr. (Heathcock) 967:22-968:5.)

As shown in Table II, Kant prepared analogues and evaluated them for tubulin binding and for *in vitro* potency. (JTX-114 at Table II.) Six analogues had a paclitaxel side chain (R2 = Ph) and four had a docetaxel side chain (R2 = t-BuO). (*Id.*) In a head-to-head comparison, compounds with the docetaxel side chain were more potent in the tubulin binding as well as in their IC_{50} data. (Tr. (Heathcock) 899:23-906:8; JTX-114 at 5545-46 (CabRef0001266-67).)

j. Kingston 1994 (JTX-107)

The Kingston paper ("Kingston 1994"), published in 1994, is a chapter in *Taxane Anticancer Agents* (Georg), which discusses both general taxane SAR and synthesis. Kingston 1994 provides a diagram of the taxane core detailing what chemical modifications (if any) are tolerated at each position. (Tr. (Roush) 1449:2-1450:1; JTX-107 at 214 (CabRef0001038).)

k. Klein (JTX-110)

The Klein paper ("Klein"), published in 1994, is a chapter in *Taxane Anticancer Agents* (Georg), and discloses 9(R)-dihydrotaxanes and the activities of numerous analogs having the 9(R)-dihydro structure. (Tr. (Heathcock) 906:14-909:10; JTX-110, Klein at 281 (CabRef0001294).) Klein prepared and evaluated analogs in which the C-7 hydroxy groups are alkylated. (Tr. (Heathcock) 906:20-906:25.)

l. Lampidis (DTX-2241)

The Lampidis paper ("Lampidis") was published in 1989 and teaches that a strategy for overcoming Pgp-mediated resistance in cancer cells was to increase the lipophilicity and, therefore, cell permeability of a drug, which would then, in effect, overwhelm the Pgp efflux mechanism. (DTX-2241 at 4271.) This results in increased concentration of the drug in the cell which could eventually kill the cell. (Tr. (Heathcock) 878:11-21; DTX-2241 at 4271 (CabRef0005374).) Dr. Ludueña acknowledged that the Lampidis reference indicates that an increase in lipophilicity likely increases the ability of the compounds to accumulate in and then kill multidrug-resistant cells. (DTX-2724 (Ludueña) at Clips 200-01.)

m. Ojima 1994 (JTX-104)

The Ojima paper ("Ojima 1994"), published in 1994, is a chapter in *Taxane Anticancer Agents* (Georg), authored by Dr. Ojima and scientists from RPR. Some of the co-authors of the

paper were researchers at RPR. (Tr. (Heathcock) 888:22-889:4). The Ojima 1994 reference teaches that using small lipophilic groups at C-10 improved performance against resistant cancer cells. (*Id.* at 888:22-889:11, 890:14-892:2; JTX-104 at 272-73 (CabRef0001097-98).) Dr. Ludueña testified that Ojima 1994 shows that taxanes can be modified chemically to improve their performance in certain multidrug-resistant cell lines. Dr. Ludueña also acknowledged that CabRef1098 teaches that modification at the C-10 position could improve performance in a multidrug-resistant cell line. (DTX-2724 (Ludueña) at Clips 172-73.)

n. Riou (JTX-98)

The Riou paper ("Riou"), published in 1992, discloses the use of a specialized cancer cell line, P388/DOX, selected to over-express Pgp. (Tr. (Heathcock) 838:3-840:12, 867:4-870:19; JTX-98 at 164-170 (CabRef0001443-49).) By comparing the activities of taxanes against resistant P388/DOX and normal P388 cancer cells, it showed that docetaxel was more potent than paclitaxel in resistant cells. This taught that docetaxel is less recognized than paclitaxel by Pgp and was less likely to be ejected from the cell by Pgp. (Tr. (Heathcock) 867:4-868:4, 870:3-19; JTX-98 at 67-168 (CabRef0001446-47).) Riou also confirmed that overexpression of Pgp was a cause of resistance to taxane compounds in cell lines. (Tr. (Heathcock) 868:5-869:1; JTX-98 at 167-68 Table IV (CabRef0001446-47).) Dr. Kingston testified that a POSA would conclude that docetaxel is better than Taxol against normal cell lines and docetaxel is "way better" than Taxol at the P388/DOX drug-resistant cell line. (Tr. (Kingston) 137:20-138:18.) Dr. Ludueña testified that it was "certainly possible" based on Riou that reduced affinity for Pgp could lead to improved performance of a drug like Taxotere in drug-resistance cell lines. (DTX-2724 (Ludueña) at Clips 130-31.)

o. Verweij (JTX-29)

The Verweij paper ("Verweij"), published in 1994, describes the mechanism of action of taxanes. (Tr. (Heathcock) 830:23-833:9, 836:22-838:2; JTX-29 at 495-505 (CabRef0001719-29).) Verweij explains that binding of taxanes enhances polymerization of the tubulin into stable microtubules. (Tr. (Heathcock) 831:17-23.) Verweij reported that docetaxel was more potent than paclitaxel in about six different kinds of cancer cells, including two mouse cell lines and five human tumor cell lines. (Tr. (Heathcock) 836:22-838:2; JTX-29 at 496 (CabRef0001720).) Docetaxel was also more potent than paclitaxel in *in vivo* animal studies. (Tr. (Kingston) 138:19-147:11; Tr. (Heathcock) 837:16-838:2; JTX-29 at CabRef0001721-25.)

p. Wils (JTX-31)

The Wils paper ("Wils") is entitled "Polarized transport of docetaxel and vinblastine medicated by Pglycoprotein in human intestinal epithelial cell monolayers." (JTX-31.) Wils was published in 1994 by RPR and confirmed that the mechanism of action for multidrug resistance in docetaxel is mediated by Pgp. (Tr. (Heathcock) 865:6-866:15; JTX-31, Wils at 1528-30 (CabRef0001782-84); DTX-2725 (Ojima) 64:22-23, 65:1-2, 65:3-7, 65:10-11; DTX-2724 (Ludueña) at Clips 136-37).)

q. Wong (JTX-115)

The Wong patent ("Wong"), entitled "7-0-Ethers of Taxane Derivatives," was invented by chemists at Bristol-Myers Squibb. (JTX-115; Tr. (Kingston) 220:1-4.) Wong generally discloses 7-ethers of taxane derivatives, including multiple taxane derivatives having a methyl ether group at the C-7 position. (JTX-115 at 1:44-64 (CabRef0001702).)

4. Obviousness

Defendants did not demonstrate obviousness by clear and convincing evidence. The Court finds that a POSA would have selected either docetaxel or paclitaxel as a lead compound, which does not foreclose Defendants' case. Defendants, however, failed to demonstrate that a POSA would have been motivated to simultaneously modify docetaxel with a methyl ether at the C-7 and C-10 positions to arrive at cabazitaxel. This is fatal to Defendants' position on obviousness. In addition, the Court finds that the secondary considerations weigh in favor of Plaintiffs. The Court will discuss each in turn.

a. Selection of Lead Compound

The Court finds that a POSA would have selected either docetaxel or paclitaxel as a lead compound. Dr. Kingston testified that: docetaxel was better than paclitaxel at the equivalent doses for patients in ovarian cancer studies; docetaxel was better than paclitaxel with respect to Phase II breast cancer studies; with one exception, docetaxel was better than paclitaxel with respect to several other types of cancer; docetaxel was better than paclitaxel with respect to a doxorubicin-resistant breast cancer; and a POSA would conclude that docetaxel is better than paclitaxel in almost every situation. (Tr. (Kingston) 145:1-147:11.) Dr. Heathcock similarly testified that a POSA would chose docetaxel as a lead compound. (Tr. (Heathcock) 843:3-8.) The Court found the testimony of Drs. Kingston and Heathcock credible with respect to the fact that a POSA may have selected docetaxel as the lead compound. In addition, Dr. Roush acknowledged that certain prior art publications showed that docetaxel was more potent in a variety of cell lines. (Tr. (Roush) 1284:15-17.)

Nevertheless, Dr. Kingston acknowledged that he selected paclitaxel as the lead compound for one of his patents during the relevant time period. (Tr. (Kingston) 196:21-197:4.) In addition,

Dr. Ojima testified that there was interest in modifying both paclitaxel and docetaxel during the relevant time period and that he used docetaxel as a lead compound. (DTX-2725 at Clips 4-5, 31-32.) Based on the testimony and the prior art references, which reflect selection of both paclitaxel and docetaxel as a lead compound, the Court finds that a POSA would have selected either docetaxel or paclitaxel as a lead compound.

b. Simultaneous Modifications with Methyl Ether at C-7 and C-10 Positions

The Court has considered the testimony and evidence and finds that Defendants have failed to demonstrate that a POSA would have been motivated to make simultaneous modifications of docetaxel with a methyl ether at the C-7 and C-10 positions. Neither Dr. Kingston's nor Dr. Heathcock's theories persuaded the Court. Rather, the Court finds that both theories are based on impermissible hindsight analysis.

Dr. Kingston testified regarding a number of prior art references, including Golik, Wong, and Kant. Four compounds disclosed in the '577 patent, Examples 1, 3, 14(b), and 15, were tested in animals. (Tr. (Kingston) 22:19-24:8.) Of the four compounds that were tested *in vivo*, Examples 14(b) and 15 are structurally similar to Example 1(a), except they have either the docetaxel side chain or the docetaxel side chain with a "prodrug" modification on the C-2' location. (Tr. (Kingston) 218:2-219:16; Tr. (Roush) 1365:21-1367:8.) The four compounds that were tested *in vivo*, however, were not tested in animals with resistant tumors. (*Id.*) In addition, although *in vivo* data is provided for other compounds, no *in vivo* data is provided for Example 1(a). (Tr. (Kingston) 215:1-5; Tr. (Heathcock) 972:23-25; Tr. (Roush) 1365:6-20.)

Golik disclosed that Example 1(a) was more active than docetaxel and paclitaxel in a single resistant cell line. (Tr. (Heathcock) 895:18-896:1; Tr. (Roush) 1363:20-1364:19.) Example 1(a), however, contained a MTM group, a unique chemical group that is three atoms long and contains

a sulfur atom. Cabazitaxel contains a methoxy group that is one atom long and contains no sulfur atom. (Tr. (Heathcock) 969:23-970:10; Tr. (Roush) 1363:20-1364:9.) In addition, there is no evidence in Golik that the methoxy group in cabazitaxel would confer a similar benefit as the MTM in Example 1(a). (Tr. (Roush) 1368:2-25.) Furthermore, Dr. Kingston acknowledged that Golik did not test the methyl ether substitution at C-7. (Tr. (Kingston) 171:16-18.)

Wong discloses and claims derivatives of docetaxel and paclitaxel and provides *in vivo* testing for several compounds, all of which have an acetyl group at the C-10 position. (Tr. (Kingston) 224:1-5.) Wong Example 2 is not the most active compound tested in Wong; Wong Example 8 is more potent. (JTX-115 at 9:15-28 (Table I); Tr. (Kingston) 221:5-21; Tr. (Roush) 1371:7-20.) Wong Example 8 has a modification to the C-2' of the side chain and a methoxymethyl group on C-7. (Tr. (Roush) 1369:12-1370:13.) Wong does not disclose any compound with the C-10 hydroxyl found in docetaxel or the C-10 methoxy found in cabazitaxel. (Tr. (Kingston) 224:6-11.) Wong also does not provide data on resistant cell lines. (Tr. (Roush) 1371:2-6.)

With respect to the Golik and Wong patents, Dr. Kingston testified that a POSA would notice that the patents together pointed towards improved activity if the OH group at C-7 is converted to an O-methyl group. (Tr. (Kingston) 179:1-9.)

Kant discloses a series of paclitaxel and docetaxel analogs modified at the C-10 position, along with tubulin binding data and IC_{50} data in one sensitive cancer cell line. (JTX-114 at 5545; Tr. (Kingston) 224:19-225:8; Tr. (Roush) 1347:14-23.) Kant does not disclose or discuss: (1) data in any sensitive cell line other than HCT 116 (Tr. (Kingston) 205:17-206:3, 245:5-12; Tr. (Roush) 1349:13-1351:8); (2) data in resistant cell lines (JTX 114 at 5545; Tr. (Roush) 1351:5-8; Tr. (Kingston) 225:6-14); or (3) drug metabolism, toxicity, or solubility, which are properties that could be modified when structural changes are made (Tr. (Heathcock) 847:25- 848:12). Additionally,

Kant does not provide any data for docetaxel and, therefore, does not establish whether any of its compounds perform better or worse than docetaxel. (Tr. (Kingston) 159:13-14; Tr. (Roush) 1352:17-1353:4.)

Dr. Kingston's testimony with respect to Kant included a discussion of Table 2, for which Dr. Kingston testified that Compound 20 was the outstanding compound. (JTX 117; Tr. (Kingston) 156:4-158:23.) Kant Compound 18, however, which provides more information to the POSA than the tubulin test, could be considered the best compound in the cellular assay. (JTX-114 at 5545 (Table II comparing Kant Compound 18 with Compound 20); Tr. (Kingston) 236:13-16; Tr. (Roush) 1351:14-1352:5, 1356:3-22.) Kant also discloses that Compound 22 is more active than paclitaxel, but Compound 22 does not include one of the changes necessary to reach cabazitaxel. (JTX-114 at 5546.)

Dr. Kingston testified that because Kant did not report results on docetaxel, he gathered data about docetaxel to include as a comparator to Compound 20. (Tr. (Kingston) 159:13-23.) Dr. Kingston imported docetaxel data from experiments in other publications. (*Id.* at 159:15-23; Tr. (Roush) 1353:5-1354:3.) Dr. Kingston found that Kant Compound 20 was better than docetaxel in tubulin ratio and HCT 116 cytotoxicity. (Tr. (Kingston) at 164:6-9.) The change that made Kant Compound 20 better was "the simple conversion of the OH group of docetaxel to the O methyl group of Compound 20." (*Id.* at 164:12-13.) According to Dr. Kingston, a POSA would "conclude that making a methyl ether at the C-10 position was a very positive step to take." (*Id.* at 164:17-10.)

Kant does not disclose or discuss compounds modified at the C-7 position, including the C-7 methoxy found in cabazitaxel. In addition, all of the compounds in Kant have a C-7 hydroxyl group. (JTX-114 at 5545; Tr. (Kingston) 225:23-25; Tr. (Roush) 1347:24-1348:3.)

Dr. Kingston concluded that a POSA would combine the teachings and make changes at both C-7 and C-10 because:

> it's a well-known principle of medicinal chemistry that if you make a change at position A and it improves activity, you make a change at position B and it improves activity. If you make that change at both positions, A and B, you'd expect an additive effect to get even better activity. This is known as the additivity principle of medicinal chemistry.

(Tr. (Kingston) 179:13-19.) Dr. Kingston also testified that a POSA would have a reasonable expectation of success that making the changes to C-7 and C-10 would result in an improved compound. (*Id.* at 179:20-24.)

Dr. Heathcock's testimony focused on Pgp as a mechanism of resistance and the modifications a POSA would be motivated to make to docetaxel in order to address the Pgp resistance issues. (Tr. (Heathcock) 858:19-897:19.) Dr. Heathcock discussed a number of prior art references, including Klein, Hait, Lampidis, and Ojima.

Klein discloses a series of C-9 modified hydroxyl compounds. (JTX-110; Tr. (Roush) 1357:4-11.) All Klein compounds have the C-10 hydroxyl or aceteyl group found in paclitaxel and docetaxel, respectively. (JTX-110 at 280-81; Tr. (Roush) 1357:4-19, 1360:10-18.) Klein teaches that its "9(R)-dihydrotaxanes show great promise as a second generation class of agents in that they have greater solubility and stability and also show excellent *in vivo* activity in several solid tumor models." (JTX-110 at 276.) A POSA would have considered this teaching. (Tr. (Roush) 1359:16-1360:1, *see also id.* at 1357:20-1359:15.) Klein does not disclose or discuss compounds modified at the C-10 position, including the C-10 methoxy found in cabazitaxel, or data for compounds modified at that position. (JTX-110 at 280-81; Tr. (Heathcock) 933:8-17.) In addition, Klein does not disclose or discuss data in resistant cell lines. (Tr. (Heathcock) 968:14-19;

Tr. (Roush) 1361:13-15.) Klein also does not disclose or discuss Pgp or how to avoid Pgp. (Tr. (Heathcock) 968:17-19.)

Hait discusses compounds called phenothiazines, which are antipsychotic compounds and differ from taxanes in size and chemical structure. (Tr. (Roush) 1334:1-1337:20; DTX-2725 at 267:18-269:16; DTX-2724 at 208:4-14.) Hait was not cited in any prior art taxane references, including the references discussed by Defendants' experts. (Tr. (Kingston) 227:16-228:19.) In addition, Hait provides only a hypothetical binding model for a protein called calmodulin, which is different from and unrelated to Pgp. (JTX-102 at 104 (Fig. 2); Tr. (Roush) 1334:1-25; DTX-2725 at 104:10-15.) Furthermore, Defendants apply Hait's hypothetical model to substrates rather than inhibitors, as taught by Hait. (Tr. (Roush) 1332:12-1333:25; Tr. (Heathcock) 887:14-888:1.)

Lampidis discusses a series of charged rhodamine dye compounds in certain MDR cells. (DTX-2241 at 4267.) Lampidis concludes that "positively-charged" dye compounds being made more lipophilic accumulate at higher levels in MDR cells. (DTX-2241 at 4271; Tr. (Heathcock) 953:20-955:8.) Lampidis, however, does not discuss taxane compounds. (DTX-2241; Tr. (Heathcock) 879:5-7.) Taxane compounds do not have a positive charge like the Lampidis compounds. (Tr. (Heathcock) 954:12-955:5.)

Ojima 1994 discloses a series of taxane compounds with modifications in the C-13 side chain, which includes the C-3' position. (JTX-104 at 272-73; Tr. (Heathcock) 966:2-19.) Dr. Ojima tested several of his modified taxane compounds in a resistant breast cancer cell line (*i.e.*, MCF7-R). (JTX-104 at 273, Table IV; Tr. (Heathcock) 863:19-864:6, 955:13-16.) As of 1994, changes to the C-3' position, and, particularly, using C-3' alkyl and alkenyl groups, were a new development for modifying taxane compounds in an attempt to address resistance. (JTX-104 at 273.) Ojima 1994 does not teach that making the "Northern Hemisphere" of docetaxel more

lipophilic increases activity in resistant cancer cells. (JTX-104; Tr. (Heathcock) 889:5-11, 891:5-892:2.) As evidenced by Ojima 1994, changes to the side chain can modulate activity in resistant cell lines. (Tr. (Heathcock) 959:18-21; JTX-104 at 273, Table IV.)

Dr. Heathcock focused on only two of Dr. Ojima's compounds: SB-T-1101 and SB-T-1102. (Tr. (Heathcock) 890:22-892:21.) Dr. Ojima's SB-T-1101 compound differs structurally from docetaxel only in the side chain. (Tr. (Heathcock) 956:6-17.) The "core" of the molecule is the same as docetaxel. (*Id.* at 955:17-21.) Dr. Ojima's SB-T-1102 compound, which was identified as "noteworthy," had improved activity in resistant cancer cells and differs structurally from paclitaxel only in the side chain. (JTX-104 at 273; Tr. (Heathcock) 956:14-20.) The "core" of the molecule is the same as paclitaxel. (*Id.* at 955:22-956:20.) In his direct testimony, Dr. Heathcock did not discuss Dr. Ojima's SB-T-1212, which was also identified as "noteworthy."[13] (JTX-104 at 273.) Dr. Heathcock acknowledged that SB-T-1212 only differs from paclitaxel at the side chain. (Tr. (Heathcock) 959:2-5.)

Dr. Heathcock concluded that a POSA would be led to the conclusion that changing the hydroxyl groups at C-7 and C-10 to methoxy groups would be expected to accomplish the goals of improving cell permeability or reducing Pgp affinity. (Tr. (Heathcock) 897:16-19.)

The Court did not find credible the lines of reasoning employed by Dr. Kingston and Dr. Heathcock in order to reach simultaneous methoxy adjustments at the C-7 and C-10 positions. Dr. Kingston and Dr. Heathcock were both knowledgeable with respect to the subject areas. In particular, they provided strong testimony with respect to the underlying science and had a good

[13] The reference states, in relevant part, "*It is noteworthy that SB-T-1102 and SB-T-1212 show one order of magnitude better activity than paclitaxel and docetaxel against MCF7-R. This finding may provide significant information for the development of newer antitumor agents effective against drug-resistant tumors.*" (emphasis in original). (JTX-104 at 273.)

understanding of the prior art references. Nevertheless, the Court finds that based on their selection of prior art references and the specific portions of those references upon which they relied, Dr. Kingston and Dr. Heathcock each "cherry-picked" his way to cabazitaxel. Here, the Court finds that their testimony fell short in their respective leaps from their selected prior art references to their ultimate obviousness conclusions. While Dr. Kingston and Dr. Heathcock took different paths to their obviousness conclusions, it was clear to the Court from their testimony that "all paths led to cabazitaxel." In effect, Dr. Kingston and Dr. Heathcock both engaged in impermissible hindsight analysis.

The Court, on the other hand, found credible Dr. Roush's testimony regarding the experimentation process and the modifications that were being made at multiple positions on the taxane molecule. (Tr. (Roush) 1258:1-1259:2.) In addition, the Court affords weight to Dr. Roush's interpretation of Hait's hypothetical model. (*Id.* at 1332:12-1333:25.) The Court also found Dr. Ludueña's testimony credible. During his video-taped deposition, Dr. Ludueña recognized and acknowledged the findings of several prior art references. (*See generally* DTX-2724.) For example, Dr. Ludueña acknowledged that the combined teachings of Riou and Wils suggest that to overcome docetaxel's resistance, one strategy might be to reduce the recognition or affinity of docetaxel for Pgp. (*Id.* at Clips 143-44.) In addition, Dr. Ludueña readily conceded that as of 1995, there was some evidence that Pgp was overexpressed in cancer cells as compared to healthy cells. (*Id.* at Clip 184.) Dr. Ludueña also testified that a POSA "would do a survey and say, 'There [are] several [known] mechanisms [of resistance]. Pgp sounds real[ly] interesting. I'll work on that. But I may also want to work on some other things.'" (*Id.* at Clip 122.)

Here, Defendants demonstrated that the issue of Pgp overexpression presented an area of interest for research during the relevant time period. The testimony regarding the prior art references Defendants relied upon, however, does not demonstrate obviousness. As discussed above, the testimony presented on behalf of Defendants reflects improper hindsight analysis. Here, in light of the fact that modifications were being made at multiple positions, including the C-2, C-4, C-5, C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-2', and C-3' positions, the Court finds that a POSA would have been motivated to make modifications on the C-7 or C-10 position. Defendants, however, failed to demonstrate that a POSA would have been motivated to make the simultaneous methoxy substitutions at the C-7 and C-10 positions required to form cabazitaxel.

c. Secondary Considerations

The Court will next examine the secondary considerations. The Court commences its analysis with a presumption of a nexus between the '170 patent and the following secondary considerations: unexpected properties, failure of others, and commercial success. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016) ("[T]here is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'") (citations omitted).

(1) Nexus with the claimed invention

The Court finds Plaintiffs' argument that "Jevtana is both an embodiment of, and coextensive with, Claims 1 and 2 of the '170 patent," valid. (Pls.' Post-Trial Br. 34, ECF No. 280.) Defendants do not contest this argument. (Defs.' Post-Trial Br. 52-57, ECF No. 264-1.)

The burden, therefore, shifts to Defendants to rebut the presumption of a nexus. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000) ("[I]f

the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus."). "The presumed nexus cannot be rebutted with mere argument; evidence must be put forth." *Id.*

(2) Unexpected Properties

"To qualify as unexpected, the claimed properties or results must be different in 'kind and not merely in degree' from the results of the prior art." *Daiichi Sankyo Co. v. Mylan Pharm. Inc.*, 670 F. Supp. 2d 359, 382 (D.N.J. 2009), *aff'd sub nom. Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346 (Fed. Cir. 2010), *cert. denied*, 526 U.S. 1286 (2011) (quoting *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996)). "While a marked superiority in an expected property may be enough in some circumstances to render a compound patentable, a mere difference in degree is insufficient." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (internal quotations omitted) (quoting *In re Papesch*, 315 F.2d 381, 392 (CCPA 1963)). "When assessing unexpected properties, . . . [the Court] must evaluate the significance and 'kind' of expected results along with the unexpected results." *Bristol-Myers Squibb Co.*, 752 F.3d 967 at 977.

Plaintiffs proffer two arguments for unexpected properties: (1) the addition of methoxy groups at C-7 and C-10 positions to docetaxel results in a compound with significant improvements in its properties as compared to docetaxel; and (2) cabazitaxel's superior activity over docetaxel, with activity of five to ten times better than docetaxel, given that it is a Pgp substrate, is not merely a difference in the level of potency as compared to docetaxel but is also a difference with respect to type of body interaction. (Pls.' Post-Trial Br. 34-35.)

Defendants assert that Dr. Roush's argument that the "FDA approval [of cabazitaxel] is evidence of unexpected results" is undercut by "[t]he inventors' ability to predict clinical success for cabazitaxel, without clinical data." (Defs.' Post-Trial Br. 55.) Defendants further assert that Dr. Roush's argument that "cabazitaxel's performance against resistant cancer cells was somehow unexpected" is also unavailing because it "conflicts with prior art, which disclosed numerous examples of taxane compounds with similar structures to cabazitaxel that showed improved potency against MDR cells." (*Id.*) Defendants also argue that cabazitaxel's "better performance" in comparison to "its peers in the prior art . . . is a 'mere difference in degree'[,] insufficient to establish unexpected results." (*Id.*) Defendants argue that cabazitaxel's improved performance against resistant cells, despite being "less of a Pgp substrate" is not unexpected "given that docetaxel (a known Pgp substrate) performed better than paclitaxel against MDR cells lines." (*Id.* at 55-56.)

The Court is persuaded by Plaintiffs' argument that it was unexpected that adding methoxy groups at the C-7 and C-10 positions to docetaxel could have resulted in a compound with significant improvements in its properties as compared to docetaxel. Researchers modified thousands of taxane analogs at almost all locations around the taxane core and side chain. (Tr. (Roush) 1295:16-21, 1381:18-1382:21.) The Court finds, however, that cabazitaxel's superior activity over docetaxel, even activity that is five to ten times better, is not entirely unexpected. The prior art disclosed that certain taxanes showed improved potency against MDR cells. Those taxanes included docetaxel, which the prior art disclosed was more potent in a variety of cell lines. (Tr. (Roush) 1284:15-17.) A POSA would therefore expect that cabazitaxel would show improved potency over docetaxel but would not expect the particular degree of superiority that cabazitaxel

showed. Cabazitaxel's superior performance, therefore, cannot be said to be entirely unexpected because it differs not in kind but only in degree, from docetaxel's performance.

The case cited by Plaintiffs in support of their argument that cabazitaxel's superiority over docetaxel is an unexpected property is distinguishable from the case at bar. In *Daiichi Sankyo Co. v. Mylan Pharm. Inc.*, the court found that the drug exhibited unexpected results due to increased drug potency, in addition to insurmountable antagonism (an activity totally lacking in the other compound), drug-drug interactions, inverse antagonism, and other rehabilitative properties. *Daiichi Sankyo Co.*, 670 F. Supp. 2d at 382. Cabazitaxel's increased potency is not a new property for a taxane. Further, cabazitaxel's superior performance over docetaxel, given that it is a Pgp substrate, is also not novel because docetaxel, also a Pgp substrate, performed better than paclitaxel against MDR cell lines. The Court, therefore, declines to adopt the reasoning in *Daiichi Sankyo Co.*, and provides minimal weight to Plaintiffs' arguments regarding unexpected results.

(3) Failure of Others

"Evidence that others within the field have tried and failed to make the claimed invention can demonstrate that the invention was nonobvious." *AstraZeneca LP v. Breath Ltd.*, 88 F. Supp. 3d 326, 390-92 (D.N.J. 2015), *aff'd*, 603 F. App'x 999 (Fed. Cir. 2015). "The purpose of evidence of failure of others is to show indirectly the presence of a significant defect in the prior art, while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan." *Warner Chilcott Co., LLC v. Teva Pharm. USA, Inc.*, 89 F. Supp. 3d 641, 672 (D.N.J. 2015), *aff'd*, 642 F. App'x 996 (Fed. Cir. 2016) (citing *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1081-83 (Fed. Cir. 2012)).

Plaintiffs argue that cabazitaxel is one of only three taxane compounds ever to receive FDA approval and remains the last such compound to be approved despite attempts by multiple groups

around the world to develop taxanes into new anticancer treatments. (Pls.' Post-Trial Br. 35.) Plaintiffs assert that the taxanes which were brought to clinical trials failed either due to toxicities or lack of activity and that these worldwide failures support a finding that cabazitaxel would not have been obvious. (*Id.* at 35-36.) Defendants, on the other hand, argue that the proper standard for evaluating whether a drug is successful is whether it shows some anticancer activity, not whether it is approved by the FDA. (Defs.' Post-Trial Br. 54.)

The Court is not persuaded by Defendants' argument. Failure to obtain FDA approval is evidence of failure of others. *See Pfizer Inc. v. Teva Pharm. USA, Inc.*, 460 F. Supp. 2d 659, 662 (D.N.J. 2006) (relying on the Federal Circuit's indirect endorsement, in *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004), of the use of "'failure to obtain FDA approval' as a benchmark for an analysis under 'failure of others'").

"In deciding how to approach the issue of failure of others to solve the problem which the patented invention solved, it is appropriate methodology to first state the problem[.]" *Pfizer Inc.*, 460 F. Supp. 2d at 662. Multiple groups around the world tried unsuccessfully to develop taxanes into effective therapies (Tr, (Sartor) 1490:8-10) and only Plaintiffs succeeded in developing a compound that showed superior activity over docetaxel, namely cabazitaxel, and obtained FDA approval. (*Id.* at 1528:1-9.)

The Court finds that Plaintiffs' success, where others had failed, in consideration of the state of the prior art during relevant time frame, points to a finding of non-obviousness and, thus, gives considerable weight to Plaintiffs' argument on this point.

(4) Commercial Success

"When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the

patent, it is presumed that the commercial success is due to the patented invention." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (quoting *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997)). However, "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006).

The Court finds that Jevtana has achieved commercial success. Dr. Tate testified that Jevtana's sales from 2010 to the end of 2016 totaled approximately $975 million in the United States and $2.1 billion worldwide. (Tr. (Tate) 666:20, 668:15-17.) Dr. Tate also testified that, based on the estimated sales for 2017, the total sales figure is expected to reach [redacted] in the United States and approximately $[redacted] worldwide, respectively. (*Id.* at 666:20-667:3, 668:19-21.) This success was also in the relevant market. Plaintiffs defined Jevtana's relevant market as "post-docetaxel mCRPC" because Jevtana can only be given to patients who have previously taken docetaxel. In addition, even with the inception of two key competitors in this market in 2013, Jevtana's market share [redacted] (*Id.* at 676:21-677:2.) It is not necessary for Jevtana to command the greatest market share. *See Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 923 F. Supp. 2d 602, 679 (D. Del. 2013), *aff'd*, 752 F.3d 967 (Fed. Cir. 2014) (quoting *Takeda Chem. Indus., Ltd. v. Mylan Labs. Inc.*, 417 F. Supp. 2d 341, 386 (S.D.N.Y. 2006)) ("There is no requirement that the invention be the only successful product in its market niche or the most successful.").

The Court finds that Defendants' argument fails because although there are multiple patents that cover Jevtana in the FDA's Orange Book, Plaintiffs successfully demonstrated, with evidence of Jevtana's performance in the "post-docetaxel mCRPC market" that Jevtana's

commercial success is due to Claims 1 and 2. The Court, therefore, affords considerable weight to Plaintiffs' argument with respect to commercial success.

Based on the foregoing, the Court finds that Defendants have failed to demonstrate obviousness by clear and convincing evidence.

5. Obviousness-Type Double Patenting

Obviousness-type double patenting is a judicially created doctrine that precludes one person from obtaining more than one valid patent for an obvious modification of the same invention. *Otsuka Pharma. Co. v. Sandoz, Inc.*, 678 F.3d 1297-98 (Fed. Cir. 2012). The Court finds that Claim 2 of the '470 patent covers docetaxel and Claim 6 of the '470 patent covers a pharmaceutical composition of docetaxel. (JTX-119 at col. 10., ll. 30-33, 42-45.) The Court further finds that because cabazitaxel is not an obvious modification of docetaxel, Defendants have failed to demonstrate obviousness-type double patenting by clear and convincing evidence.

IV. '592 PATENT

A. Post-Trial Filings

1. Summary

Subsequent to the conclusion of the bench trial on November 8, 2017, the parties filed several items of correspondence. Plaintiffs' November 17, 2017 correspondence indicated that: (1) Plaintiffs were not appealing the Board's determination of the unpatentability of Claims 1-5, 7-20, and 22-29; (2) the USPTO would issue and publish a certificate canceling those claims after the time for appeal expired on November 24, 2017; and (3) as of November 24, 2017, any remaining arguments by Defendants as to the validity or non-infringement of those claims would become moot. (Pls.' 11/17/17 Ltr., ECF No. 285.)

Defendants' December 4, 2017 response to Plaintiffs' correspondence asserted that the invalidity and non-infringement of the asserted claims remained ripe for decision. (Defs.' 12/4/17 Ltr., ECF No. 298.) According to Defendants, they presented evidence of invalidity and non-infringement on the '592 patent claims that Plaintiffs originally asserted at trial and, therefore, are entitled to receive a decision on their counterclaims. (*Id.*) Defendants also argued that there continues to be a substantial controversy between the parties sufficient to support Article III jurisdiction over Defendants' Declaratory Judgment counterclaims because Plaintiffs seek to amend claims as part of their appeal of the IPR decision. (*Id.*) Defendants argue that if Plaintiffs receive narrower, amended claims through the IPR process, a judgment of invalidity or non-infringement from this Court as to the originally asserted claims would preclude Plaintiffs from asserting those narrower claims against Defendants as a matter of law. (*Id.*)

On December 11, 2017, Plaintiffs filed correspondence indicating that they filed a statutory disclaimer with the USPTO pursuant to 35 U.S.C. § 253 and 37 C.F.R. § 1.321(a). Plaintiffs asserted that the statutory disclaimer becomes part of the original patent, and Claims 7, 11, 14-16, and 26 are now viewed as though they "never existed." (Pls.' 12/11/17 Ltr., ECF No. 300.) Defendants' December 11, 2017 responsive correspondence argued that there continues to be a substantial controversy between the parties sufficient to support Article III jurisdiction over Defendants' Declaratory Judgment counterclaims with respect to Claims 7, 11, 14-16, and 26 of the '592 patent. (Defs.' 12/4/17 Ltr., ECF No. 298.)

Because the parties' correspondence contained minimal case law citations and legal analysis, the Court required the parties to brief the issues raised in the correspondence. (12/12/17 Letter Order, ECF No. 302.) The parties filed legal briefs on December 13, 2017. (Pls.' Br., ECF No. 303; Defs.' Br., ECF No. 304.) The Court has reviewed and carefully considered the parties'

positions and finds good cause to issue a decision with respect to Claims 7, 11, 14-16, and 26, as set forth below.

2. Discussion

a. The Court's Jurisdiction

The Court has carefully considered the parties' submissions and is unpersuaded by Plaintiffs' arguments. The Supreme Court has stated that the standard for determining whether a declaratory judgment action satisfies the case or controversy requirement of Article III is "whether the facts alleged,[14] under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *MedImmune, Inc. v. Genetech, Inc.*, 549 U.S. 118, 127 (2007) (quoting *Md. Cas. Co. v. Pac. Coal & Oil Co.*, 312 U.S. 270, 273 (1941)). There is no bright-line rule that dictates which cases satisfy the requirement and which do not. *MedImmune, Inc.*, 549 U.S. at 127. The issues raised in the case "must be 'definite and concrete, touching the legal relations of parties having adverse legal interests'; and . . . be 'real and substantial' and 'admi[t] of specific relief through a decree of a conclusive character, as distinguished from an opinion advising what the law would be upon a hypothetical state of facts.'" *Id.* (quoting *Aetna Life Ins. Co. v. Haworth*, 300 U.S. 227, 240-41 (1937)) (alteration in original).

Here, the parties conducted an entire trial of this case. On September 21, 2017, after the trial was underway, the PTAB issued its decision with respect to the '592 patent. (Defs.' 9/21/17 Letter, ECF No. 21.) On the final day of the trial, Plaintiffs simply indicated that they "were going to focus Dr. Sartor's examination . . . on Claims 21 and 30." (Tr. 1480:9-13.) Defendants

[14] The district court in the *MedImmune* case disposed of the declaratory judgment claims on its grant of a motion to dismiss. *MedImmune, Inc. v. Genetech, Inc.*, 549 U.S. 118, 120 (2007).

responded that they "continue[d] to ask for a judgment of invalidity on all of the claims that have been a part of the case." (*Id.* at 1480:16-22.) Plaintiffs did not object. In addition, Plaintiffs did not move at any time prior to the conclusion of the trial to voluntarily dismiss their assertion of Claims 7, 11, 14-16, and 26. The current procedural posture of the case also reflects that the claims at issue have not been cancelled. The Court, therefore, finds that it has subject matter jurisdiction over Claims 7, 11, 14-16, and 26.

b. Additional Legal Standards

(1) Infringement

The patentee bears the burden of proving infringement. *Medtronic, Inc. v. Mirowski Family Ventures, LLC*, 134 S. Ct. 843, 846 (2014). In the event that the patentee fails to offer evidence to rebut a counterclaim of non-infringement, the patent infringer may be entitled to a declaratory judgment or summary judgment. In *Medtronic*, the Supreme Court held that when a licensee seeks a declaratory judgment against a patentee to establish that there is no infringement, the burden of proving infringement remains with the patentee—the burden never shifts to the patent infringer. *Id.* Several practical considerations support the patentee's burden requirement: (1) shifting the burden based on the form of action could create post-litigation uncertainty about a patent's scope; (2) compelling a licensee to prove a negative may create unnecessary complexity; and (3) burden shifting is difficult to reconcile with the Declaratory Judgment Act's purpose of ameliorating the "dilemma" posed by requiring one challenging a patent's scope to choose between abandoning rights or risking suit. *MedImmune*, 549 U.S. at 129.

In *Apple, Inc. v. Samsung Electronics Co.*, the court granted the alleged patent infringer's motion for judgment as a matter of law that the products at issue did not infringe the patent because the patentee had the burden to demonstrate infringement but presented no evidence. 67 F. Supp.

3d 1100, 1125-27 (N.D. Cal. 2014), *aff'd*, 816 F.3d 788 (Fed. Cir. 2016), *vacated in part on reh'g en banc*, 839 F.3d 1034 (Fed. Cir. 2016). The court held that although Samsung presented no evidence at trial on the issue of infringement as to the products, it was clear that both Apple and Samsung expected to try the issue of infringement as to those products and that these claims were not akin to claims merely "referenced in the complaint." *Id.* Relevant to the court's consideration was the fact that Apple was forced to prepare its defense in advance of trial and had to try the case for three weeks. *Id.* Finally, the court found that Samsung's dismissal of its claim of infringement did not moot Apple's counterclaim. *Id.* The court, therefore, found that the issue of non-infringement was "fairly placed in issue" such that Apple was entitled to a determination on its counterclaim. *Id.*

In *Radware, Ltd. v. A10 Networks, Inc.*, the court granted the alleged patent infringer's motion for summary judgment of non-infringement on all claims that the patentee no longer asserted because: (i) the patentee's original infringement contentions asserted every claim; and (ii) the alleged patent infringer's declaratory judgment counterclaims were directed to all of the same claims. Case Nos. C-13-02021; C-13-02024, 2014 WL 2738538, at *9 (N.D. Cal. June 11, 2014). The Court noted that the patentee bore the burden of proving infringement under *Medtronic, Inc.*, and did not meet this burden; thus, the alleged patent infringer was entitled to summary judgment of non-infringement as to the claims that the patentee no longer asserted. *Id.*; *but see Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180 (Fed. Cir. 2014) (holding that judgment was not warranted because the patents were not litigated or fairly placed in issue during the trial). Here, the Court finds that Claims 7, 11, 14-16, and 26 were fairly placed in issue during the trial and the Court may issue a judgment with respect to such claims.

(2) Invalidity

"Where a declaratory judgment action asserts invalidity of patents, the Supreme Court of the United States has admonished that the issue of validity should be considered and not avoided by dispositions based on non-infringement grounds." *Windmoller v. Laguerre*, 284 F. Supp. 563, 565 (D.D.C 1968). "When an alleged infringer attacks the validity of an issued patent, well-established law places the burden of persuasion on the attacker to prove invalidity by clear and convincing evidence." *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008).

"A patent is presumed valid, and the burden of persuasion to the contrary is and remains on the party asserting invalidity." *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1303 (Fed. Cir. 2008) (quoting *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1573 (Fed. Cir. 1985)); *see also Research Corp. Techs. v. Microsoft Corp.*, 627 F.3d 859, 870 (Fed. Cir. 2010) (same). "[T]he party asserting invalidity also bears the initial procedural burden of going forward to establish a legally sufficient *prima facie* case of invalidity. If this burden is met, the party relying on validity is then obligated to come forward with evidence to the contrary." *Ralston Purina Co.*, 772 F.2d at 1573 (alteration in original). "Rebuttal is merely 'a showing of facts supporting the opposite conclusion,' and may relate to any of the *Graham* factors including the so-called secondary considerations." *ABB Air Preheater, Inc. v. Regenerative Envt'l Equip. Co.*, 167 F.R.D. 668, 673 (D.N.J. 1996).

The trial court has the responsibility to determine whether the challenger has met its burden by clear and convincing evidence. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007) (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1534 (Fed. Cir. 1983)). The trial court considers the totality of the evidence, including any rebuttal evidence presented by the

patentee. *Id.* Clear and convincing evidence exists when the movant "place[s] in the mind of the ultimate fact finder an abiding conviction that the truth of its factual contentions [is] 'highly probable.'" *Medinol Ltd. v. Guidant Corp.*, 412 F. Supp. 2d 301, 312 (S.D.N.Y. 2005) (alteration in original); *see also Buildex Inc. v. Kason Indus., Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988) ("The 'clear and convincing' standard of proof of facts is an intermediate standard which lies somewhere between 'beyond a reasonable doubt' and a 'preponderance of the evidence.'" (citing *Addington v. Texas*, 441 U.S. 418, 425 (1979)).

B. Testimony

1. Sunil Gupta

Dr. Gupta, an Associate Vice-President of Global Regulatory Affairs and Head of Sanofi LLC's North American Region for Regulatory Affairs, is the sole inventor of the '592 patent and testified by means of video deposition excerpts. (Gupta Video Day 1 Clip 1-2; DTX-2723 Clip 11.) Dr. Gupta testified regarding the '592 patent and the clinical trials using cabazitaxel. (*See generally* DTX-2722.) He stated that he had no involvement in the Phase I or Phase II clinical trials conducted on cabazitaxel and first became involved with cabazitaxel in 2005. (*Id.* at Clips 6, 9.) Dr. Gupta also testified that he led the multinational team through the preparation and filing of the NDA related to cabazitaxel. (*Id.* at Clip 8.) Dr. Gupta testified that several decisions were made in parallel with respect to the '592 patent: (1) the 25 mg/m^2 dose; (2) the three per week schedule as opposed to a weekly schedule; and (3) combining the cabazitaxel with prednisone. (*Id.* at Clips 43, 54.) Dr. Gupta testified that he did not recall any journal articles or publications that praised the work performed in developing the inventions claimed in the '592 patent or reading any articles or publications describing a need for a drug like the one he invented. (*Id.* at Clips 78-79.)

2. Rachel A. Hansard[15]

Rachel Hansard, the director of solid tumor marketing at Sanofi, testified by means of video deposition excerpts regarding a number of marketing-related issues. (*See generally* DTX-2721.) Ms. Hansard testified that Jevtana and its competitors, [redacted] (JTX-2721 Clip 4.) In addition, Ms. Hansard testified that she considered Jevtana to be [redacted] (*Id.* at Clip 8.) Ms. Hansard also testified that the jump in Jevtana's sales figures from 2010 to 2011 represented long-felt need. (*Id.* at Clips 17-18.) According to Ms. Hansard, "there [were] a significant number of patients at that time that had progressed on or after docetaxel that were waiting for Jevtana to be approved by the FDA. And that is representative of the long[-]felt need." (*Id.* at Clip 18.) Ms. Hansard testified that Jevtana arguably has [redacted] *Id.* at Clip 28.) Ms. Hansard testified that Jevtana [redacted] (*Id.* at Clips 33, 85.) In addition, Ms. Hansard testified about Jevtana's commercial rebate program. (*Id.* at Clips 36-39.) When asked whether there have been any losses on Jevtana and whether Jevtana is profitable for Sanofi, Ms. Hansard testified "I don't know." (*Id.* at Clips 41-44.)

3. DeForest McDuff, Ph.D.[16]

Dr. McDuff testified on behalf of Defendants with respect to commercial success. Dr. McDuff testified regarding the basis for his opinions that: (1) Jevtana sales have not been

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[15] Ms. Hansard was designated by Sanofi as a Rule 30(b)(6) witness on topics relating to Sanofi's sales and marketing of the cabazitaxel product. (FPT Order Sec. 6, Pls.' Witnesses § A.1.)

[16] Dr. McDuff, a partner at Insight Economics, has more than ten years of experience in consulting, finance, and economic research, including in more than forty litigations involving

commercially successful; and (2) there is a lack of nexus between the commercial performance of Jevtana and the '592 patent. (Tr. (McDuff) 716:13-22.)

Dr. McDuff testified that Jevtana's sales are somewhat unimpressive and relatively low compared to benchmarks, including competitors as well as the industry generally. (Tr. (McDuff) 719:22-25.) Dr. McDuff also testified that: (1) two competitive products that came on the market after Jevtana, Xtandi and Zytiga, significantly outperformed Jevtana with sales in excess of $2 billion a year (*id.* at 726:18-23, 737:10-11); (2) Jevtana's sales show that it is not a top selling or impressive drug in the industry and its sales are even below average for new drug products (*id.* at 730:5-8); (3) Jevtana is not a top selling oncology drug and not capturing much of that market (*id.* at 732:25-733:4); and (4) Jevtana is [redacted] (*id.* at 761:6). Upon cross-examination, Dr. McDuff acknowledged that there are two separate patient populations, pre-docetaxel and post-docetaxel. (*Id.* at 770:8-19.) In addition, Dr. McDuff testified that he was not offering an opinion as to nexus with respect to the '170 patent. (*Id.* at 771:2-4.)

4. Daniel P. Petrylak, M.D.[17]

Dr. Petrylak testified on behalf of Plaintiffs that he reviewed the '592 patent for two issues: (1) to determine whether Jevtana or cabazitaxel is covered by the particular patent; and (2) whether Defendants' proposed use of cabazitaxel encourages and causes the practice of methods related to the '592 patent. (Tr. (Petrylak) 515:18-23.) Dr. Petrylak testified that there are no differences

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pharmaceuticals. Dr. McDuff has Bachelor's degrees in economics and mathematics from University of Maryland, a Master's degree in economics from Princeton University, and a Ph.D. in economics from Princeton University. (Tr. (McDuff) 713:9-715:2.)

[17] Dr. Petrylak was accepted as an expert with respect to the treatment of prostate cancer and the evaluation of prostate cancer treatments. (Tr. (Petrylak) 514:25-515:6.)

between Defendants' labels and Jevtana's label and that it is only necessary to look at one product label as representative of all Defendants' labels.[18] (*Id.* at 525:1-4, 525:13-16.)

Dr. Petrylak testified that there is more than one corticoid that is used with Defendants' product: dexamethasone and prednisone are both used, and both are prescribed by an attending physician. (*Id.* at 535:16-20, 537:4-6, 537:19-21.) Both corticoids are part of a pre-medication regimen that is used half an hour before cabazitaxel is administered. (*Id.* at 535:25-536:2.) The pre-medication regimen consists of three different components: an antihistamine, dexamethasone, and an H2 blocker. (*Id.* at 536:3-5.)

Dr. Petrylak testified that giving dexamethasone prior to cabazitaxel is considered "in combination with cabazitaxel" because "even though [dexamethasone is] given a half an hour before[, it] is still in the system, it's still affecting the cells that may cause the anaphylaxis, it's affecting a variety of different areas, so it is still present." (*Id.* at 536:21-537:3.) With respect to prednisone, Dr. Petrylak testified that Defendants' label instructs the physician to prescribe to the patient 10 mg of prednisone in combination with cabazitaxel, and it is either administered in one dose or two different dosages. (*Id.* at 537:19-538:10.) The doctor writes the prescription, but the patients take the prednisone themselves (*id.* at 358:13-16), unlike the dexamethasone that is administered by an infusion nurse at the infusion center (*id.* at 533:24-534:7). Dr. Petrylak testified that Section 17 of Defendants' label, entitled "Patient Counselling and Information," explains the importance of prednisone to the patient and provides that if they do not take the prednisone, they are to report it to their physician. (*Id.* at 539:7-14.) Furthermore, Dr. Petrylak testified that prednisone has anti-inflammatory effects that can help control patients' pain and help them feel

[18] For the purpose of his testimony, Dr. Petrylak choose Fresenius's label (PTX-1023). (*Id.* at 525:17-20.)

better. (*Id.* at 539:25-540:2.) He noted that studies have demonstrated prednisone's activity against prostate cancer, but there has not been a study testing cabazitaxel without prednisone and he does not know the effect of cabazitaxel absent the prednisone. (*Id.* at 540:5-10.)

Dr. Petrylak testified that the 1989 Tannock paper (JTX-38) explains the importance of prednisone. (*Id.* at 540:11-19.) Dr. Petrylak also testified that Tannock found that 38% of patients with castration-resistant prostate cancer taking prednisone had some improvement in various quality of life parameters (*e.g.*, pain, energy, appetite, and fatigue), lasting between three and thirty months with a median duration of four months, and 19% of these patients maintained this improvement. (*Id.* at 540:22-541:4, 541:24-542:3.) Next, Dr. Petrylak testified that Defendants' label (PTX-1363) indicates that prednisone has significant anti-inflammatory effects. (*Id.* at 541:8-16.) Dr. Petrylak concluded that the Fresenius label: (1) instructs the physician to tell patients to report when they do not take prednisone; and (2) advises patients to report to the physician when they do not take prednisone. (*Id.* at 544:19-24.)

Dr. Petrylak acknowledged on cross examination that Tannock was not a randomized trial establishing that prednisone was an effective anticancer agent and that the aim of the study was palliation. (*Id.* at 556:5-12.) Furthermore, Dr. Petrylak acknowledged that the study: (1) provided little evidence of a consistent anticancer response from prednisone (*id.* at 556:16-21); (2) provided no convincing evidence that systemic therapy with prednisone improves the survival of patients with metastatic prostate cancer and that further measures of symptom control should be used to assess palliation (*id.* at 557:2-9); and (3) is clearly insufficient for FDA-approved prednisone to be considered as an anticancer therapy (*id.* at 557:10-13). Dr. Petrylak also acknowledged that prednisone has not been approved by the FDA to treat cancer as a single agent and that, as a single agent in a control trial, prednisone is likely palliative. (*Id.* at 557:14-560:25). Dr. Petrylak testified

that out of the hundreds of times he prescribed cabazitaxel, only once did he decline to prescribe prednisone to a patient. (*Id.* at 569:15-17.) Dr. Petrylak stated that cabazitaxel is not lethal with respect to safety and efficacy if administered to a patient who is not taking prednisone. (*Id.* at 563:3-10.)

Dr. Petrylak additionally testified that he understands the Jevtana data is applicable to Defendants' products through Defendants' bioequivalence waivers PTX-1014, PTX-1025, PTX-1060, PTX-1076, PTX-1143, PTX-1208 and PTX-1244. (*Id.* at 547:9-15.)

Dr. Petrylak testified that element D of Claim 21, which states "wherein the prostate cancer is a castration-resistant or hormone-refractory metastatic prostate cancer," instructs the physician to give cabazitaxel to these types of patients and it does so within the "indications and usage section" of the Defendants' label. (*Id.* at 552:4-11.)

Dr. Petrylak concluded that Defendants' label will cause a physician to infringe the '592 asserted claims because the label:

> is a guideline for physicians to direct and control the administration of cabazitaxel, and that's seen in the label for both the physician who directs the infusion nurse, as well as the patient who is going to receive the drug and then administer the prednisone to themselves. The nurses are absolutely required to follow what the physician says and the directions of the physician in the situation. And, again, to control side effects and to control the outcome, the patients must follow what the physician says as far as the prednisone or potentially suffer adverse events that are related to lack of prednisone. [D]efendants' labels direct and encourage the use of methods claimed in the '592 patent, and the physician, in fact, uses all of these methods to treat the patients, and these are very desperately ill patients that must follow these protocols exactly.

(*Id.* at 553:21-554:12.)

5. Mark J. Ratain, M.D.[19]

Dr. Ratain testified on behalf of Defendants that, to a POSA, all of the asserted claims in the '592 patent would have been obvious over the prior art because there is no significant difference between the asserted claims and the prior art. (Tr. (Ratain) 305:21-4, 386:16-25). Dr. Ratain also testified that any required combinations are obvious combinations that a POSA would have been motivated to combine and that a POSA would have had a reasonable expectation of success in arriving at the asserted claims. (*Id.* at 386:19-25.) Furthermore, Dr. Ratain testified that a number of prior art references provided knowledge about cabazitaxel during the relevant time period, prior to 2009 when the compound was disclosed in the patent. (*Id.* at 334:7-16.)

With respect to the Mita study ("Mita"), a Phase I study published on January 15, 2009 (JTX-45), Dr. Ratain testified that a POSA would understand from reading Mita that cabazitaxel was developed as a solution to the multidrug resistance problem. (Tr. (Ratain) 338:2-13; 338:21-340:5.) Mita teaches a POSA that some patients will have more toxicity than others and concludes that cabazitaxel has a favorable safety profile for hematologic toxicity. (*Id.* at 443:9-14, 479:9-16.) Dr. Ratain further testified that "Mita teaches you that you could start somebody at 25 [mg/m^2] and monitor them closely, or you could start somebody at 20 [mg/m^2] and potentially escalate them." (*Id.* at 443:9-14.) Dr. Ratain acknowledged that measuring anticancer activity of cabazitaxel in prostate cancer was not the primary objective of the Mita study. (*Id.* at 408:16-25.)

[19] Dr. Ratain was accepted by the Court as an expert in treating cancer and oncology, including pharmacokinetics in clinical trials and drug development for advanced solid tumors, with experience in studying and treating prostate cancer. (Tr. (Ratain) 298:22-299:4.)

Dr. Ratain testified that the Attard[20] paper ("Attard"), published online on May 3, 2005, interpreted Mita the same way he interpreted Mita, which is the way a POSA would have interpreted Attard. (*Id.* at 348:12-350:23.) "Attard reports that cabazitaxel is not a Pgp substrate, that it's given intravenously over a one-hour infusion every three weeks, that the maximally tolerated dose is 20 [mg/m^2], that it's active in taxane refractory prostate cancer, and that it's dose from the toxicity is neutropenia." (*Id.* at 350:12-18.)

Dr. Ratain testified that the Pivot study ("Pivot"), which studied cabazitaxel in taxane resistant metastatic breast cancer patients (*id.* at 351:6-9), concludes that: (1) "cabazitaxel appears to be active in docetaxel or paclitaxel resistant breast cancer"; and (2) "the safety profile of cabazitaxel was very favorable when compared with the known safety profile of the market of taxanes or other compounds under development." (*id.* at 353:15-354:1). Dr. Ratain further testified that a POSA would understand Pivot to demonstrate the activity of cabazitaxel in a notoriously difficult population and to treat patients with diseases that are initially responsive to taxanes but then become resistant—a concept relevant to treating both breast cancer and prostate cancer. (*Id.* at 354:15-21.)

Dr. Ratain testified that he did not use hindsight analysis because even prior art such as the Beardsley paper ("Beardsley") relied on Pivot and related it to prostate cancer. (*Id.* at 354:24-355:4.) Dr. Ratain noted that the Beardsley paper relates the breast cancer in Pivot to prostate cancer and states that:

> a Phase II trial with cabazitaxel has not been performed in patients with prostate cancer; however, given its activity in the docetaxel refractory setting described above, referring to [Pivot], this agent is currently being investigated in a Phase III multi-center randomized

[20] John De Bono was the author of Attard, investigator on Mita, and co-principal investigator in the TROPIC study. (Tr. (Ratain) 428:1-9.)

> superior trial comparing three weekly cabazitaxel with prednisone to mitoxantrone with prednisone in patients with castrate-resistant metastatic prostate cancer previously treated with docetaxel-containing treatment.

(*Id.* at 356:19-357:4.) According to Dr. Ratain, a POSA, therefore, would understand that a Phase III trial has been initiated and that the rationale for the Phase III trial was the "exciting results observed for cabazitaxel in [Pivot]." (*Id.* at 357:7-11.) Dr. Ratain also testified that Beardsley described the next study, the Phase III study, to include 720 patients and was performed in May 2010. (*Id.* at 357:12-18.)

Dr. Ratain further testified that multiple publications, specifically the Rodrigues, Winquist and MacKenzie publications, published in the Canadian Journal of Urology, reported this Phase III clinical trial prior to the filing of the '592 patent application in 2009. (*Id.* at 357:19-358:15.) Dr. Ratain also testified that archived listings from clinicaltrials.gov publications (DDTX-2135 and 2136) contained details about the TROPIC trial and the annual report of GCRI, a cancer center in India, contained a description of the Phase III TROPIC trial. (*Id.* at 358:19-359:11, 365:23-366:1; DDTX-2209.)

Dr. Ratain testified that from Rodrigues, Winquist, MacKenzie, clinicaltrials.gov, and the GCRI report, a POSA would understand that cabazitaxel was being studied at a dosage of 25 mg/m^2 in combination with prednisone every three weeks for treatment of hormone-refractory prostate cancer. (Tr. (Ratain) 360:21-361:2.) Dr. Ratain also testified that even though the Rodrigues, Winquist, and MacKenzie publications do not explicitly reference anything about measuring neutrophil levels or stopping treatment if neutrophil levels fall below a certain level, a POSA would understand that "to practice as a medical oncologist[, it is implied that] one would need to monitor the neutrophils and to not administer the toxic chemotherapy drug if the neutrophil count was below [] 1,500 [cells/mm^3]." (*Id.* at 361:18-362:6.) Furthermore, a POSA "would

understand that to be eligible for the study[,] the patients would have had to previously been treated with docetaxel and demonstrate a progression of disease." (*Id.* at 367:22-25)

Dr. Ratain then provided specific testimony with respect to the various claims of the '592 patent in relationship to the prior art. He testified that Claim 1 is a method for the administration of cabazitaxel to a patient with prostate cancer and it is not limiting. He testified that the TROPIC protocol disclosures, Rodrigues, Winquist, the GCRI Report, and clinicaltrials.gov disclose: (1) that the limitation is prostate cancer that has progressed during or after treatment with docetaxel; (2) the dose of 20 to 25 mg/m^2 of cabazitaxel or a hydrate or solvate; (3) that cabazitaxel needs to be given in combination with a corticoid; and (4) the particular corticoid to be used is prednisone. (*Id.* at 369:9-370:8). Therefore, according to Dr. Ratain, "all the limitations of Claim 1 are anticipated because they are all disclosed in each of the Phase III Disclosures and these five individual references." (*Id.* at 370:11-14.) Dr. Ratain testified that because Claim 27 has the same substantive limitations as Claim 1, all the references of TROPIC protocol, the TROPIC listings have limitations in Claim 27. (*Id.* at 370:20-24.)

Dr. Ratain also testified that Claims 15, 21, 26, and 30 all add the same element to Claim 1 or Claim 27, which is the specific dosage limitation of 20 mg/m^2. (*Id.* at 379:4-7.) Furthermore, Dr. Ratain noted that there is no difference between Claims 15, 21, 26, and 30 and the prior art because: (1) 20 mg/m^2 is explicitly disclosed in both Mita and Pivot (*id.* at 379:8-14); (2) a POSA would understand that if a patient started at 25 mg/m^2 and developed unacceptable toxicity, one would need to lower the dose to 20 mg/m^2 which is an obvious reduction of 20% (*id.* at 379:14-19); and (3) the Taxotere label disclosed that the dosage shall be reduced for patients with an unacceptable toxicity from 75 mg/m^2 to 60 mg/m^2, which is a 20% reduction (*id.* at 379:20-380:2).

Dr. Ratain testified that Mita teaches that not everyone can tolerate a dose of 25 mg/m^2. (*Id.* at 380:21-22.)

Dr. Ratain testified that all of the asserted claims are obvious because there is no significant difference between the "asserted claims and the prior art; any combinations required are obvious combinations; and a POSA would be motivated to combine them and have a reasonable expectation of success in arriving at the asserted claims." (*Id.* at 386:19-25.) Dr. Ratain additionally testified that in 2006, as the basis of the Phase III study in mCRPC, Sanofi provided the FDA with the following disclosure: "based on the fact that with cabazitaxel, three responses were observed in prostate cancer patients in earlier Phase I study [Mita] and in patients whose metastatic breast cancer was resistant to prior taxanes promising activity with low incidence of adverse events [Pivot], except neutropenia, cabazitaxel is well suited for development in the second line setting in patients with hormone-refractory prostate cancer that progress after Taxotere based treatment." (*Id.* at 392:23-393:7.) According to Dr. Ratain, Sanofi informed the FDA that the Mita and Pivot studies supported the TROPIC study, which studied the hormone-refractory, docetaxel resistant prostate cancer. (*Id.* at 393:16-21.)

Dr. Ratain testified that: (1) after Mita was published, a POSA would have been focused on prostate cancer with cabazitaxel because there were two responses observed in prostate cancer; (2) by 2006, a POSA would have known that Sanofi was focused on cabazitaxel in mCRPC patients whose treatment failed on docetaxel because of the clinicaltrials.gov archive; and (3) by the time the '592 patent was filed, a POSA would have known that the "Phase III trial had been ongoing for almost three years and was scheduled to be completed in the next seven months." (*Id.* at 481:10-482:8.)

6. Alton Oliver Sartor, M.D.[21]

Dr. Sartor was an investigator on the TROPIC study that led to the FDA approval of Jevtana. Dr. Sartor testified that Claims 21 and 27 specify the corticoids, prednisone or prednisolone, which can be used in combination with 20 mg/m^2 of cabazitaxel and given to a castration-resistant or hormone-refractory metastatic prostate cancer patient that has progressed during or after treatment with docetaxel. (Tr. (Sartor) 1481:3-11.) Dr. Sartor opined that a POSA in October of 2009 would not have had a reasonable expectation that a dose of 20 mg/m^2 of cabazitaxel, in combination with a corticoid, would have anticancer activity in a patient with mCRPC who has progressed during or after docetaxel. (*Id.* at 1481:12-20.) According to Dr. Sartor, "[t]here simply was not adequate data available at this particular dose in that particular patient population." (*Id.* at 1481:21-22.)

Dr. Sartor testified that prior to 2009, "we didn't have any method that was known to prolong survival" in mCRPC patients who failed on docetaxel therapy. (*Id.* at 1485:21-1486:3, 1486:16-23.) Dr. Sartor further testified that "[t]here was an urgent need for systemic treatment options for patients with castration-resistant prostate cancer who progressed after receiving first-line docetaxel chemotherapy." (*Id.* at 1487:5-8.) Dr. Sartor also testified that prior to 2009, there were a number of compounds that had entered clinical development which were shown to overcome taxane resistance in preclinical studies in cell lines or rodent models. (*Id.* at 1489:14-21.) These included: (1) XRP6258 (cabazitaxel), by Sanofi; (2) the BMS compounds, by Bristol Myers Squibb; (3) the M compounds under development through Wyeth; and (4) the

[21] Dr. Sartor was accepted by the Court as an expert in the treatment of patients with prostate cancer, including the clinical development and evaluation of potential new methods of treating patients with prostate cancer. (Tr. (Sartor) 1474:18-24.)

Daiichi compound. (*Id.* at 1489:22-1490:2.) Dr. Sartor testified that other than cabazitaxel, none of the taxanes under clinical development were "developed into effective therapies." (*Id.* at 1490:8-11.)

Dr. Sartor also testified regarding his interpretation of Mita and Attard. (*Id.* at 1492:9-1578:24.) Dr. Sartor testified that no Phase II study was conducted with cabazitaxel in prostate cancer. (*Id.* at 1506:18-21.) In addition, Dr. Sartor testified that Sanofi's Phase II breast cancer cabazitaxel study (Pivot) concerned a different disease than prostate cancer. (*Id.* at 1506:22-25.) Dr. Sartor testified that it would be difficult for a POSA to conclude from Pivot that cabazitaxel has anticancer activity at a dose of 20 mg/m^2 in patients with taxane-resistant metastatic breast cancer. (*Id.* at 1510:5-12.) Dr. Sartor indicated that because there is "no specification of dose, it's very difficult to make a conclusion regarding the dose and the tumor shrinkage that was seen" in Pivot. (*Id.*)

On cross examination, Dr. Sartor testified that he focused his testimony on a dose of 20 mg/m^2 and only on Claims 21 and 30 even though he previously provided an expert opinion regarding other doses. (*Id.* at 1529:11-1530:14.) On cross examination, Dr. Sartor acknowledged that: (1) the FDA news release from the TROPIC study was not at 20 mg/m^2 (*id.* at 1530:19-25); (2) a dose reduction is standard in a clinical trial with a cancer agent (*id.* at 1531:2-13); (3) by looking at the Kaplain-Meier curve (*i.e.*, the survival curve) in the '592 patent, one cannot tell from the data which patients were treated with 20 mg/m^2 and which patients were treated with 25 mg/m^2 (*id.* at 1533:4); (4) the only time the '592 patent actually discusses the 20 mg/m^2 dose is for dose reductions in Column 17, Example 2 in Table 6 (*id.* at 1540:16-18; 1541:1-18); and (5) Table 5 in Column 17 of the '592 patent, which provides the results of the TROPIC study,

"suggests that the vast majority were treated at the 25 [mg/m^2]" dose and the results in the patent do not really speak to 20 mg/m^2 dose (*id.* at 1541:20-24, 1542:2-4, 1543:9).

7. Jonathan D. Schiff, M.D.[22]

Dr. Schiff testified as an expert on behalf of Defendants with respect to Jevtana's label (JTX-16). (Tr. (Schiff) 589:2-7.) Dr. Schiff testified that many of his patients do not comply with the prescribed regimen of 10 mg/day of prednisone and miss anywhere from five to six doses over a thirty-day period. (*Id.* at 596:16-597:7.) Additionally, Dr. Schiff testified that even if his patients advise him that they are not taking their prednisone as prescribed, he does not discontinue or delay their Jevtana treatment. (*Id.* at 597:8-14; 597:21-25.)

Dr. Schiff testified that if Defendants' products are approved, they will: (1) induce infringement of Claims 7, 11, 14, 15, 16, 21, 26, and 30 (*id.* at 602:1-5); and (2) contributorily infringe Claim 14 (*id.* at 602:6-10). In order to prove induced or contributory infringement, Dr. Schiff stated that Plaintiffs must first demonstrate direct infringement by showing "that either a single actor carries out all of the method steps or that a single actor directs or controls others to collectively carry out all the method steps." (*Id.* at 602:11-25.) Dr. Schiff testified that in this case there is no single actor that carries out all the method steps because the "Jevtana infusion is done in an infusion center that's typically been administered by an infusion nurse, and the prednisone is administered by the patient himself, by taking the pill orally every day." (*Id.* at 603:5-9.)

[22] Dr. Schiff was accepted by the Court as an expert in the treatment of prostate cancer, including the interactions between prostate cancer patients who have been prescribed prednisone to be taken along with docetaxel or cabazitaxel and the physicians who are treating those patients and the premedication that is given to the patients before they receive an infusion of Jevtana. (Tr. (Schiff) 587:23-588:8.)

Dr. Schiff further testified that the administration of the premedication, which includes dexamethasone, followed by the administration of cabazitaxel thirty minutes later, does not satisfy the requirements in Claims 7, 11, 21, and 26 that the cabazitaxel be administrated in combination with a corticoid because "to be given in combination as is stipulated in the [C]laims, the medication would have to be present in the patient's bloodstream throughout the duration of time of effect of the Jevtana." (*Id.* at 610:4-7.) Dr. Schiff stated that 10 mg of prednisone is given by mouth every day and "will be present and active in the patient's bloodstream if it's used in that fashion." (*Id.* at 610:7-10.)

Dr. Schiff testified that Claims 14, 15, 16, and 30 of the '592 patent do not use the term "corticoid." (*Id.* at 616:12-17.) Dr. Schiff also testified that Plaintiffs' arguments with respect to dexamethasone do not apply to Claims 14, 15, 16, and 30 of the '592 patent. (*Id.* at 616:18-21.) According to Dr. Schiff, there is no direct infringement because: (1) the doctor does not direct or control the administration of prednisone; (2) the doctor does not condition administration of Jevtana on the patient taking prednisone as prescribed; and (3) the doctor does not condition receiving the benefit of Jevtana treatments on the patient taking pre-prednisone as prescribed. (*Id.* at 616:24-617:6.) Furthermore, Dr. Schiff opined that "there is no direct infringement from the administration of dexamethasone as a premedication because administering dexamethasone once every three weeks is not in combination with cabazitaxel." (*Id.* at 617:7-10.) Finally, Dr. Schiff testified that "without an act of direct infringement, there cannot be any induced or contributory infringement." (*Id.* at 617:11-12.)

8. Michael E. Tate[23]

Michael Tate, a vice president within the intellectual property practice at the consulting firm Charles River Associates, testified on behalf of Plaintiffs with respect to commercial success. (Tr. (Tate) 654:22-25, 657:17-19.) Mr. Tate testified that he understood the analysis of commercial success to constitute a two-step process: (1) evaluate the performance of the particular product; and (2) determine whether the success can be attributed to the claimed invention. (*Id.* at 658:22-25.) Mr. Tate acknowledged that he did not analyze whether Jevtana's success can be attributed to the claimed invention. (*Id.* at 659:7-11.) Rather, his work in this matter related to the first step only. (*Id.*) Mr. Tate then testified to the basis of his opinion that Jevtana was a commercial success. (*Id.* at 659:12-677:6.) Mr. Tate found JEVTANA® to be a commercial success based upon his analysis of the products in the relevant market and considering the sales and market share of Jevtana. (*Id.* at 661:4-677:6.) In reaching his decision, Mr. Tate also considered the promotional efforts for Jevtana. (*Id.* at 675:21-676:8.)

C. Infringement

Plaintiffs demonstrated by a preponderance of the evidence that Defendants' proposed cabazitaxel products will induce infringement of Claims 21 and 30 of the '592 patent.[24]

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[23] Mr. Tate was accepted by the Court as an expert in the field of economic analysis as it pertains to commercial success. (Tr. (Tate) 657:17-22.)

[24] Because invalidity is an affirmative defense, the Court will first address the issue of infringement. The Court, however, will only address infringement of Claims 21 and 30 of the '592 patent because Plaintiffs appeared to abandon their infringement arguments as to Claims 7, 14, 15, 16, and 26 in conjunction with their decision to not rebut the evidence Defendants proffered in support of their invalidity defenses as to Plaintiffs' previously-asserted claims. Indeed, Plaintiffs' Proposed Findings of Fact and Conclusions of Law only address Claims 21 and 30 of the '592 patent. As set forth in Section IV.D, *infra*, the Court finds Claims 21 and 30 to be invalid. Nevertheless, the Court will make its Findings of Facts and Conclusion of law on infringement for purposes of a complete record.

The methods of Claims 21 and 30 have three elements: (1) administering cabazitaxel in combination with a corticoid (specifically prednisone or prednisolone for Claim 30); (2) to a patient having castration-resistant or hormone-refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel; and (3) wherein the dose of cabazitaxel is 20 mg/m^2.

Each of Defendants' proposed cabazitaxel products, if approved, will be sold with a product label (collectively, "Defendants' labels"). (PTX-1013; PTX-1023; PTX-1057; PTX-1140; JTX-20A; JTX-25; DTX-2467; Tr. (Petrylak) 523:6-15.) The purpose of a product label is to instruct physicians on the proper patients for treatment, how to treat the patients, potential side effects, and how to manage side effects. (Tr. (Petrylak) 523:16-25.) Physicians will read Defendants' labels before administering Defendants' proposed cabazitaxel products. (*Id.* at 524:1-5; Tr. (Schiff) 635:13-24.) There are no substantive differences between any of Defendants' proposed labels and the Jevtana label. (Tr. (Petrylak) 524:22-525:16; Tr. (Schiff) 600:3-10.)[25] Defendants' proposed cabazitaxel products, if approved, will be used the same way that Jevtana is used because the instructions in Defendants' labels are the same as the instructions in the Jevtana label. (Tr. (Schiff) 621:10-17.)

Defendants' labels instruct physicians to administer Defendants' proposed cabazitaxel products in combination with a corticoid as described in Claim 21. (Tr. (Petrylak) 535:21-537:6, 551:24-552:20, 553:17-554:12.) Defendants' labels instruct physicians to administer Defendants' proposed cabazitaxel products as a "one-hour intravenous infusion every three weeks in combination with oral prednisone 10 mg administered daily throughout" cabazitaxel

[25] *See also* Section I.F, *supra*, which summarizes the Stipulated Facts with respect to the product labels.

treatment. (PTX-1013 at FCAB00011922; PTX-1023 at FCAB00345171; PTX-1057 at ACCORD_CABA0064412; PTX-1140 at AAPO-CAB00013928; JTX-20A at ACCORD_CABA0066572; JTX-25 at MYL_CAB0000150; DTX-2467 at DTX-2467.3; Tr. (Petrylak) 537:15-538:12, 545:22-24, 553:17-554:12; Tr. (Schiff) 590:19-591:13.) Defendants' labels also instruct physicians to advise patients to read the Patient Information section of the label and to explain the importance of prednisone: "Explain that it is important to take the oral prednisone as prescribed. Instruct patients to report if they were not compliant with oral corticosteroid regimen." (PTX-1013 at FCAB00011937; PTX-1023 at FCAB00345187-88; PTX-1057 at ACCORD_CABA0064430; PTX-1140 at AAPO-CAB00013944-45; JTX-20A at ACCORD_CABA0066591; JTX-25 at MYL_CAB0000168-69; DTX-2467 at DTX-2467.19; Tr. (Petrylak) 539:2-17; Tr. (Schiff) 591:14-592.)

Product labels have a section directed to patients, the Patient Information section, which informs patients of the product's potential side effects and benefits. (Tr. (Petrylak) 524:6-21.) The Patient Information section of Defendants' labels informs patients that the physician will tell the patient how and when to take the prednisone, that it is "important" for the patient to take the prednisone "exactly as prescribed by your doctor," and to "make sure to tell [the] doctor or nurse" if the patient forgets to take the prednisone or does not take it on schedule. (PTX 1013 at FCAB00011940; PTX-1023 at FCAB00345191; PTX-1057 at ACCORD_CABA0064434; PTX-1140 at AAPO-CAB00013948; JTX-20A at ACCORD_CABA0066595; JTX-25 at MYL_CAB0000171; DTX-2467 at DTX-2467.21; Tr. (Petrylak) 544:3-18; Tr. (Schiff) 593:22-595:3.)

Defendants' proposed cabazitaxel products will be administered in combination with two corticoids, dexamethasone and prednisone. (Tr. (Petrylak) 535:14-20.) The terms "corticoid" and

"corticosteroid" are interchangeable. (*Id.* at 537:9-14.) Dexamethasone is a corticoid. (Tr. (Schiff) 608:14-16.) Defendants' labels instruct physicians to administer dexamethasone intravenously as part of a premedication regimen thirty minutes prior to the administration of each dose of Defendants' proposed cabazitaxel products. (PTX-1013 at FCAB00011923; PTX-1023 at FCAB00345171; PTX-1057 at ACCORD_CABA0064414; PTX-1140 at AAPO-CAB00013928; JTX-20A at ACCORD_CABA0066572; JTX-25 at MYL_CAB0000151; DTX-2467 at DTX-2467.4; Tr. (Petrylak) 535:21-536:9; Tr. (Schiff) 606:25-608:4.)

The dexamethasone premedication is given "in combination" with cabazitaxel because both drugs are present in the body at the same time. (Tr. (Petrylak) 536:21-537:3; *see also* JTX-6 at col. 6, ll. 35-60, 56-61.) The dexamethasone and cabazitaxel will be in a patient's body at the same time for a few days. (Tr. (Petrylak) 563:21-564:2.) Some physicians who prescribe cabazitaxel will infuse the drug and any premedications into the patients themselves. (Tr. (Schiff) 632:3-9.) If the prescribing physician does not infuse the cabazitaxel products, the healthcare provider who will be infusing Defendants' proposed cabazitaxel products and the dexamethasone premedication is under the direction and control of the prescribing physician. (Tr. (Petrylak) 536:18-20; Tr. (Schiff) 632:10-16.) If the infusion of cabazitaxel is performed by a nurse (or other healthcare professional), typically that same nurse will infuse the dexamethasone-containing premedication to the patient. (Tr. (Petrylak) 536:13-20, 553:17-554:12; Tr. (Schiff) 631:19-632:2.)

The patient administers the prednisone orally to himself under the direction and control of the physician. (Tr. (Petrylak) 538:3-16, 553:17-554:12.) The physician directs and controls how a patient takes prednisone (orally), how much to take (10 mg), and how often to take it (daily). (*Id.* at 537:19-539:1, 553:17-554:12; Tr. (Schiff) 634:4-24.) The prescribing physician

establishes the manner and timing of administration of prednisone based on Defendants' labels. (Tr. (Petrylak) 537:19-539:1; Tr. (Schiff) 634:4-24.)

Administration of prednisone is important for the safe and effective use of Defendants' proposed cabazitaxel products. (Tr. (Petrylak) 539:18-540:4; 553:17-554:12.) Because the Phase III TROPIC study investigated only cabazitaxel in combination with prednisone, it is not known whether patients will receive the clinical benefits reported in TROPIC from administration of cabazitaxel alone. (*Id.* at 539:18-540:10; Tr. (Schiff) 641:22-642:3.) Although it does not prolong survival as a single agent, prednisone has been reported to reduce inflammation and pain. (PTX-1363 at SA_JEV_0183327; JTX-38 at 590; (Tr. (Petrylak) 539:18-540:4, 540:11-541:20, 557:18-558:2, 558:24-559:10; Tr. (Schiff) 583:9-17, 636:15-23.) Prednisone also improves energy and increases appetite thereby counteracting the side effects of cabazitaxel, such as fatigue, nausea and vomiting. (JTX-38 at 590; Tr. (Ratain) 324:12-15; Tr. (Petrylak) 540:11-541:4, 541:21-542:3; Tr. (Schiff) 583:9-17, 636:6-637:23.)

When a patient who is scheduled to receive a cycle of cabazitaxel has not been taking his prednisone as directed and is, therefore, suffering from fatigue, physicians will often delay administration of chemotherapy until the patient is back on prednisone and feels strong enough for more chemotherapy. (Tr. (Ratain) 412:18-413:13; Tr. (Petrylak) 542:17-544:2; Tr. (Schiff) 628:21-629:4.) Dr. Petrylak had one patient out of approximately 100 that could not take prednisone. (Tr. (Petrylak) 545:2-4, 561:1-16, 562:3-24, 569:3-19.) Dr. Schiff's patients on cabazitaxel have been prescribed prednisone, and none have refused to take it. (Tr. (Schiff) 583:9-11, 604:24-605:2, 633:22-25.) If a patient has not been taking prednisone and does not advise the physician, physicians will likely know anyway due to changes in the patient's physical appearance. (Tr. (Petrylak) 545:2-21; Tr. (Schiff) 639:1-10.)

Defendants' labels instruct physicians to administer Defendants' proposed cabazitaxel products in combination with prednisone as described in Claims 21 and 30 and to condition the benefit of Defendants' proposed cabazitaxel products for at least some patients on the patient taking prednisone. (Tr. (Petrylak) 542:4-544:2, 551:24-552:20, 552:25-553:3, 553:17-554:12.)

In addition, Defendants' labels instruct physicians to administer Defendants' proposed cabazitaxel products to patients having hormone-refractory metastatic prostate cancer who have progressed during or after a docetaxel-containing treatment regimen. (PTX-1013 at FCAB00011922, FCAB00011935; PTX-1023 at FCAB00345171, FCAB00345185; PTX-1057 at ACCORD_CABA0064412, ACCORD_CABA0064427-28; PTX-1140 at AAPO-CAB00013928, AAPO-CAB00013942-43; JTX-20A at ACCORD_CABA0066572, ACCORD_CABA0066589; JTX-25 at MYL_CAB0000150, MYL_CAB0000166; DTX-2467 at DTX-2467.3, DTX-2467.16-17; Tr. (Petrylak) 526:21-527:16, 528:2-22, 551:25-552:20, 552:25-553:3; Tr. (Schiff) 581:7-13, 589:19-590:8.) There are no other approved uses for cabazitaxel. (Tr. (Schiff) 621:6-9.)

Defendants' proposed cabazitaxel products, if approved and marketed, will be administered at a dose of 20 mg/m^2 to at least some patients. (Tr. (Petrylak) 531:23-532:2, 532:7-13; Tr. (Schiff) 629:11-630:1.) Defendants' labels instruct and will inevitably lead to the administration of cabazitaxel in combination with a corticoid (including prednisone) to patients having castration-resistant or hormone-refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel at a cabazitaxel dose of 20 mg/m^2, in accordance with the methods of Claims 21 and 30. Defendants' labels instruct physicians that the patient should receive a dose of 20 mg/m^2 of cabazitaxel if he experiences certain side effects on the recommended dose of 25 mg/m^2. (PTX-1013 at FCAB00011922-23; PTX-1023

at FCAB00345171-72; PTX-1057 at ACCORD_CABA0064412-13; PTX-1140 at AAPO-CAB00013928-29; JTX-20A at ACCORD_CABA0066573; JTX-25 at MYL_CAB0000150-51; DTX-2467 at DTX-2467.3-4; Tr. (Petrylak) 529:21-532:2; Tr. (Schiff) 627:19-628:13.)

Dr. Schiff acknowledged on cross examination that he is not a medical oncologist, does not have training in medical oncology, has never been involved in any research involving chemotherapy in the treatment of prostate cancer, has never published on the use of chemotherapy in the treatment of prostate cancer, has never taught classes specifically relating to oncology, has never written a prescription for cabazitaxel because if one of his patients develops mCRPC he refers them to a medical oncologist, and does not have intimate knowledge of what happens at an infusion center other than his experience with his father, what his patients tell him and his discussion with his colleagues. (Tr. (Schiff) 618:2-619:20.) Dr. Schiff also conceded that if Defendants' cabazitaxel products are approved, they will be used in the same way that Jevtana is used because the instructions in Defendants' product labels are the same as the instructions in the Jevtana label. (*Id.* at 621:9-17.) Also, Dr. Schiff acknowledged that the person doing the premedication infusion, which includes the corticoid dexamethasone, is under the control of the physician. (*Id.* at 632:10-20.) In addition, Dr. Schiff acknowledged that patients taking cabazitaxel had all previously been on docetaxel and that docetaxel is only given in combination with prednisone. (*Id.* at 637:8-14.) Dr. Schiff also testified that he recommends that his patients with mCRPC that have progressed on docetaxel receive cabazitaxel with prednisone. (*Id.* at 639:15-20.) During certain portions of his testimony, it also appeared that Dr. Schiff attempted to revisit the Court's previous claim construction analysis.[26] (*Id.* at 608:17-609:3, 610:4-7.)

[26] Defendants did not raise the "in combination with the corticoid" element for claim construction. Furthermore, in its decision on one of Defendants' *in limine* motions, the Court denied Defendants' alternative request to reopen claim construction at this late stage of the proceeding.

The Court, on the other hand, found Dr. Petrylak's testimony both credible and persuasive and credits significant weight to his testimony. Here, the Court finds that Plaintiffs demonstrated by a preponderance of the evidence that Defendants' proposed cabazitaxel products will induce infringement of Claims 21 and 30 of the '592 patent.

D. Invalidity

1. POSA

Plaintiffs assert that a POSA for the '592 patent would possess the following qualifications: (a) a medical degree; (b) board-certification in medical oncology; (c) experience treating prostate cancer patients including patients with metastatic disease; and (d) experience evaluating prostate cancer therapies. (Tr. (Petrylak) 516:11-517:6; Tr. (Sartor) 1481:23-1482:7.) Defendants acknowledge that the parties generally agree that the POSA would be an individual (or team) with a working knowledge of clinical oncology and training in medical oncology, and would have experience with cancer patients. (Tr. (Ratain) at 301:3-302:3.) According to Defendants, while there are subtle differences between the parties' definitions, the analysis is the same regardless of which definition is used. The Court finds the proposed POSA definitions substantially similar and the differences inconsequential and declines to adopt either definition.

2. Prior Art

The prior art to the '592 patent includes:

a. Attard (JTX-42)

Attard, entitled "Update on tubulin-binding agents," is a review article on tubulin binding agents, which is the class of anticancer agents that encompasses taxanes and other antimitotic drugs. (JTX-42). Attard interpreted the positive results in Mita to mean that cabazitaxel "may overcome some forms of . . . tumor resistance." (Tr. (Ratain) 349:15-25; JTX-42 at 75.) Table 3

of Attard noted that cabazitaxel is not a Pgp substrate, and is active in taxane-refractory CRPC tumors. (JTX-42 at 75).

b. Beardsley (DTX-2090)

Beardsley, entitled "Systemic therapy after first-line docetaxel in metastatic castration-resistant prostate cancer," was published in 2008. (Tr. (Ratain) 354:24-355:12; DTX-2090.) The paper discloses treatment options after failure of docetaxel in patients with castration-resistant prostate cancer, and specifically references Pivot, noting that cabazitaxel is being investigated in Phase III trials for docetaxel-resistant metastatic castration-resistant prostate cancer. (Tr. (Ratain) 355:13-357:4.)

c. Mita (JTX-45)

Mita, entitled "Phase I and Pharmacokinetic Study of XRP6258 (RPR116258A), a Novel Taxane Administered as a 1-Hour Infusion Every 3 Weeks in Patients with Advanced Solid Tumors," was published on January 15, 2009. (Tr. (Ratain) 334:17-335:2; JTX- 45). The Mita paper discloses the use of cabazitaxel in clinical trials based on encouraging cytotoxic antitumor activity in cancer cell lines expressing a multidrug-resistant phenotype. (Tr. (Ratain) 338:25-339:14).

d. Mitoxantrone Label (JTX-37)

The mitoxantrone label was published in the 2006 Edition of the Physician's Desk Reference, which is a compendium of all FDA-approved drug labels for the convenience of the physician. (Tr. (Ratain) 325:22-25.) The mitoxantrone label reported that grade 4 neutropenia occurred in 54% of hormone-refractory prostate cancer patients receiving mitoxantrone. (JTX- 37 at 3162; Tr. (Sartor) 1573:14-1574:3.) The mitoxantrone label also reported that mitoxantrone was administered together with 10 mg/day of prednisone. (JTX-37 at 3159; Tr. (Ratain) 326:15-19.)

e. The Phase III Disclosures— Winquist (DTX-2391), Rodrigues (DTX-2316), and the GCRI Report (DTX-2209)

Several details of the TROPIC study were published prior to October 2009, including in Winquist (DTX-2391), Rodrigues (DTX-2316), and the GCRI Report (DTX-2209) (collectively "Phase III Disclosures").

The Winquist article, entitled "Open clinical uro-oncology trials in Canada," was published in February 2008 and disclosed the ongoing Phase III TROPIC study using cabazitaxel. (Tr. (Ratain) 358:6-18, 363:2-22; DTX-2391 at 3948.) The Rodrigues article, entitled "Open Clinical Uro-oncology Trials in Canada," was published in 2007 and disclosed Sanofi's multi-center study for the administration of 25 mg/m^2 of XRP-6258 in combination with prednisone every three weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. (Tr. (Ratain) 360:3-361:2; DTX-2316, Rodrigues at 3784 (CabRef0002996).)

The GCRI Report was published in August 2008 and describes the ongoing clinical trial as "[a] randomized, open label multi-center study of [cabazitaxel] at 25 mg/m^2 in combination with prednisone every three weeks compared to Mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere-containing regimen." (Tr. (Ratain) 365:11-366:1; DTX-2209 at 78 (CabRef0002789).) The GCRI Report also disclosed that the TROPIC study included monitoring of neutrophil counts in all patients. (Tr. (Ratain) 366:26-17; DTX-2209 at 79 (CabRef0002790).)

Each of the Phase III Disclosures disclosed that the TROPIC study involved administration of cabazitaxel with prednisone. (Tr. (Ratain) 363:10-13.) In addition, each of the Phase III Disclosures discloses a method for treating patients with hormone-refractory metastatic prostate

cancer previously treated with docetaxel to increase overall survival by providing 25 mg/m^2 cabazitaxel with prednisone. (*Id.* at 361:2-17; 363:2-6, 367:19-25.)

f. **Pivot** (JTX-47)

Pivot, entitled "A multicenter phase II study of XRP6258 administered as a 1-h i.v. infusion every 3 weeks in taxane-resistant metastatic breast cancer patients," was published in 2008. (Tr. (Ratain) 350:24-351:9; JTX-47.) Pivot reports activity of cabazitaxel in taxane-resistant metastatic breast cancer patients, using a starting dose of 20 mg/m^2. (Tr. (Ratain) 350:24-351:9, 353:13-18, 354:6-21.)

g. **Taxol® Label** (DTX-2361)

The Taxol® label was last revised in February of 2000, and instructs physicians on how to prescribe paclitaxel. (DTX-2361 at 6.) The Taxol® label reported that neutropenia occurred in 90% of patients, and grade 4 neutropenia occurred in 52% of patients receiving paclitaxel. (DTX-2361 at 3.) The Taxol® label also instructed physicians to reduce the dose of paclitaxel by 20% in case of severe neutropenia. (DTX-2361 at 5.)

h. **Taxotere® Label** (JTX-56)

The Taxotere® Label (JTX-56) was last revised in September of 2007, and instructs physicians how to prescribe docetaxel. (JTX-56 at 1.) The Taxotere® Label indicated that the recommended dose of docetaxel to treat prostate cancer was 75 mg/m^2, and instructed to reduce the dose of docetaxel by 20% from 75 mg/m^2 to 60 mg/m^2 in the case of unacceptable toxicity. (JTX-56 at 6; Tr. (Ratain) 312:7-10, 329:2-18.) Such dose reductions would often be used in patients with febrile (accompanied by fever) or prolonged grade 4 neutropenia (neutrophil levels less than 500 cells/mm^3). (Tr. (Ratain) 329:2-22; JTX-56 at 6.) Grade 4 neutropenia occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/ m^2 of docetaxel. (JTX-56 at

11; Tr. (Ratain) 312:1-10.) Because the standard dose of docetaxel for prostate cancer is 75 mg/m^2, grade 4 neutropenia is an expected side effect of docetaxel treatment. (Tr. (Ratain) 312:11-19.) The Taxotere® label reported that docetaxel was administered together with 10 mg/day of prednisone. (JTX-56 at 4; Tr. (Ratain) 328:18-329:1.)

3. The Asserted Claims Are Invalid

a. Claims 21 and 30

The '592 patent is directed to the use of a 20-25 mg/m^2 dose of cabazitaxel to treat mCRPC. (JTX-6.) Claim 21 states, "The method according to claim 20, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m^2." (JTX-006, column 20, lines 22-24.) Claim 21 depends from Claim 20, which depends from Claim 1. Claim 20 requires that the prostate cancer is a castration-resistant or hormone-refractory, metastatic prostate cancer. Claim 21 adds the additional limitation requiring the dose of cabazitaxel to be 20 mg/m^2. Claim 30 states, "The method according to claim 27, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m^2." (JTX-006, column 20, lines 37-39.) Claim 30 depends from Claim 27, and requires the dose of cabazitaxel to be 20 mg/m^2. Based on the Court's previous claim construction, the claim preamble is not limiting. Accordingly, efficacy is not a requirement of the claims as construed. Claims 1 and 27, therefore, are anticipated by the Phase III Disclosures. (Tr. (Ratain) 369:17-370:24.)

The TROPIC trial was a trial done at a dose of 25 mg/m^2 of cabazitaxel. (Tr. (Sartor) 1532:20-1533:2.) The 20 mg/m^2 dose was not studied in the TROPIC trial except as a dose reduction in a small percentage of patients. (*Id.*) Accordingly, the results of the TROPIC trial do not tell a POSA specific and detailed information about a 20 mg/m^2 dose. (*Id.* at 1533:14-24; 1534:14-18.) Nevertheless, a POSA would expect the TROPIC trial to include a dose reduction,

like the standard 20% dose reductions instructed in the docetaxel and paclitaxel labels. (DTX-2361, Taxol label at 5 (CabRef0003458); JTX-56, Taxotere label at 7 (CabRef0003466).) Twenty percent is a typical dose reduction because physicians still want the dose administered to have some efficacy. (Tr. (Ratain) 330:3-13.) Dr. Sartor acknowledged that dose reductions are relatively standard events within chemotherapy trials. (Tr. (Sartor) 1531:10-13.) Furthermore, Dr. Sartor acknowledged that a POSA would know about the 20% dose reduction that was used with other taxanes, and would "conjecture" that the same dose reduction was used in the TROPIC trial. (*Id.* at 1546:25-1547:10.)

A POSA would have been motivated to start patients at risk for complications at a 20 mg/m^2 dose, rather than at the higher 25 mg/m^2 dose. (Tr. (Ratain) 379:8-19.) Mita recommended a 20 mg/m^2 dose for further development because of the toxicities associated with a 25 mg/m^2 dose. (JTX-45 at 727 (CabRef0002902).) Mita also disclosed activity in the form of a partial response for both a 15 mg/m^2 dose and a 25 mg/m^2 dose. (JTX-45 at Table 3 (CabRef0002901).) In addition, Pivot noted that cabazitaxel was "active and well-tolerated" at a dose of 20 mg/m^2. (JTX-47 at 1547 (CabRef0002984).)

The Court found Dr. Ratain's testimony both credible and persuasive. Dr. Ratain provided a clear summary of the prior art. Moreover, Dr. Ratain's expert testimony was strongly supported by the evidence of record and the Court found Dr. Ratain's opinions to be well-reasoned, logical, and internally consistent. The Court, therefore, affords great weight to Dr. Ratain's testimony.

The Court, on the other hand, found that Dr. Sartor lacked credibility with respect to the key aspect of his testimony, the 20 mg/m^2 dose. Rather, the Court found Dr. Sartor's testimony to be litigation-inspired. For example, Dr. Sartor attempted to explain why the PTAB misunderstood his position in the PTAB proceeding. (Tr. (Sartor) 1475:16-1476:14.) Dr. Sartor also responded

numerous times during cross examination that he could not remember or was trying to remember. (*See, e.g., id.* at 1544:9-10, 1549:21, 1550:3-5, 1550:17-20, 1553:3-4, 1553:7-9, 1553:12, 1559:2-6, 1565:19-21, 1593:9-10.) In addition, Dr. Sartor's testimony regarding the 20 mg/m^2 dose in relationship to the prior art references was not persuasive. (Tr. (Sartor) 1509:21-1510:12, 1532:15-19). Dr. Sartor testified that the TROPIC trial was started at 25 mg/m^2 and that there was a built-in dose reduction to 20 mg. (*Id.* at 1531:2-6.) Dr. Sartor acknowledged that "there were prescribed dose reductions built in depending on certain toxicities or events that occurred during the [clinical] trial." (*Id.*) Dr. Sartor also conceded that a dose reduction is a relatively standard event within a chemotherapy trial.[27] (*Id.* at 1531:21-22.) The Court, accordingly, affords minimal weight to Dr. Sartor's testimony.

With respect to secondary considerations, Plaintiffs do not argue that there is a presumption of nexus between the '592 patent and secondary considerations. (*But see* Pls.' Post-Trial Br. 33-34 (arguing that there is a presumed nexus between the '170 patent and secondary considerations because the Jevtana patent is both an embodiment of, and coextensive with, Claims 1 and 2 of the '170 patent).) Plaintiffs argue only that unexpected results support the nonobviousness of Claims 21 and 30. (Pls.' Post-Trial Br. 52.)

Plaintiffs assert that while Dr. Sartor's involvement in the Tropic trial was met with initial skepticism by his colleagues, experts' responses to the results of the Trial were "[h]ugely positive." (Tr. (Sartor) 1522:9-14, 1527:4-14.) Plaintiffs also assert that the results of the Tropic trial were unexpected because "[the Tropic trial] was more likely to fail than succeed given the unpredictability in the art and given that [the Tropic trial] patients received another taxane despite

[27] The Court recognizes that even Dr. Petrylak acknowledged on cross examination that he has "dose reduced patients to 20 [mg/m^2]." (Tr. (Petrylak) at 567:16-17.)

being docetaxel-resistant." (Pl.'s Post-Trial Br. 53.) Plaintiffs further argue that while "the FDA expedited cabazitaxel availability based primarily on [the results of the] TROPIC [trial], cabazitaxel is used today at a dose of 20 mg/m^2 to prolong patient lives," and that "[t]he unexpected survival benefit at that dose is further evidence that the methods of Claims 21 and 30 were nonobvious as of October 2009." (*Id.* at 54.)

Defendants argue that there is no nexus between any alleged secondary consideration and the '592 patent because "Dr. Sartor never testified about the nexus and Mr. Tate 'specifically testified that he did not consider the question of nexus.'" (Defs.' Post-Trial Br. 52.) Defendants also argue that "even if [Plaintiffs] were to argue that Jevtana is an embodiment of the claims and thus nexus is presumed," there is no nexus to Claims 21 and 30 of the '592 patent because "[t]he data presented in the patent that Sanofi relies on is directed to the 25 mg/m^2 dose, . . . [and] that there is no independent data on the 20 mg/m^2 dose", which "appears in the '592 patent only as a dose reduction from 25 mg/m^2." (*Id.*)

The Court is not persuaded by Plaintiffs' arguments. "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (quoting *In Re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)). Plaintiffs rely on the TROPIC trial, which involved the administration of cabazitaxel to some patients and mitoxantrone to others, to support their argument of unexpected results. (Pls.' Post-Trial Br. 52-54.)

As Defendants correctly point out, however, the Phase III Disclosures, and not the Tropic trial, were the closest prior art. (Defs.' Post-Trial Br. 56; Tr. (Ratain) 398:5-8.) Even if the Court considers the TROPIC trial as the closest prior art, Plaintiffs' argument is still unavailing because it was not unexpected that cabazitaxel would outperform mitoxantrone, which did not have a

history of improving survival. (Tr. (Ratain) 399:10-12.) Plaintiffs' argument that "[t]he unexpected survival benefit at [the 20 mg/m^2] dose is further evidence that the methods of Claims 21 and 30 were nonobvious as of October 2009" (Pls.' Post-Trial Br. 54) does not prevail because the TROPIC trial expressly included a dose reduction from 25 mg/m^2 to 20 mg/m^2 (Tr. (Sartor) 1532:20-1533:2), which is a typical dose reduction that considers the retention of efficacy. (Tr. (Ratain) 330:3-13; Tr. (Sartor) 1546:25-1547:10.) In addition, the Court found Dr. McDuff's testimony persuasive with respect to the "lack of nexus between the commercial performance of Jevtana and the '592 patent." (Tr. (McDuff) 716:18-20.) Here, the Court finds that Plaintiffs failed to demonstrate nexus.

The Court, thus, gives little weight to Plaintiffs' argument, having found an absence of nexus between the '592 patent and unexpected results. (Tr. (Tate) 698:11-16; *See Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327 (Fed. Cir. 2008) ("[A] nexus between the merits of the claimed invention and evidence of secondary considerations is required in order for the evidence to be given substantial weight in an obviousness decision.").

Based on the factual findings set forth above, the Court finds that Defendants have demonstrated by clear and convincing evidence that Claims 21 and 30 of the '592 patent are obvious in view of the prior art. 35 U.S.C. § 103.

b. Claims 7, 11, 14, 15, 16, and 26

The Court will examine each of the claims that Plaintiffs asserted going into the trial, despite that immediately prior to the last day of trial, Plaintiffs elected not to present testimony regarding such claims.

(1) Claim 7

Claim 7 states, "The method according to claim 1, wherein said cabazitaxel, or hydrate or solvate thereof, is administered in an amount to provide an AUC of about 991 ng•h/mL (CV

34%)." (JTX-006, column 19, lines 3-5.) Claim 7 depends from Claim 1 and recites the additional limitation that the cabazitaxel "is administered in an amount to provide an AUC of about 991 ng•h/mL (CV 34%)." AUC is a pharmacokinetic parameter that measures the area under the concentration-time curve for a drug. (Tr. (Ratain) at 313:12-25.)

Defendants met the procedural burden of establishing a legally sufficient *prima facie* case of invalidity with respect to Claim 7. As Dr. Ratain testified, the claimed AUC value is the natural result of administering 25 mg/m^2 of cabazitaxel and, therefore, is anticipated by the Phase III Disclosures. (*Id.* at 371:13-372:13.) In addition, Claim 7 is rendered obvious by the AUC disclosure in Mita of 1,038 +/- 299 µg•h/L for the 25 mg/m^2 dose of cabazitaxel (JTX-45 at 729), which is approximately the same as the claimed value of 991 µg•h/L (CV 34%). (Tr. (Ratain) at 372:21-373:9.) Accordingly, Plaintiffs were obligated to come forward with evidence to the contrary. *See Ralston Purina Co.*, 772 F.2d at 1573 (alteration in original). Plaintiffs, however, failed to present evidence to the contrary.

Based on the factual findings set forth above, Defendants have shown by clear and convincing evidence that Claim 7 of the '592 patent is invalid as obvious in view of the prior art. 35 U.S.C. § 103.

(2) Claim 11

Claim 11 states, "The method according to claim 10, further comprising discontinuing cabazitaxel treatment in a patient with a neutrophil count of ≤1,500 cells/mm^3." (JTX-006, column 19, lines 15-17.) Claim 11 depends from Claim 10, which depends from Claim 1, and adds the limitation that blood counts be monitored and neutrophil levels be measured in the patient.

Defendants met the procedural burden of establishing a legally sufficient *prima facie* case of invalidity with respect to Claim 11. Defendants asserted that Claim 11 was obvious in view of Mita, Pivot, the Phase III Disclosures, the docetaxel label and based on the standard of care, as

found in the docetaxel and taxol labels. Dr. Ratain testified that monitoring blood counts and measuring neutrophil levels are part of the standard of care inherent in providing chemotherapy. (Tr. (Ratain) 327:22-25.) Dr. Ratain also testified that a POSA would have expected that threshold to be used in the TROPIC trial. (*Id.* at 374:12-376:5.) The GCRI Report also disclosed that blood counts be monitored and neutrophil levels be measured in the patient in the TROPIC trial. (DTX-2209 at 79 (CabRef0002790); Tr. (Ratain) 366:2-17.) In addition, many chemotherapy drugs, including docetaxel, mitoxantrone, and paclitaxel, had labels that instructed physicians to cease treatment if neutrophils dropped below 1,500 cells/mm^3. (JTX-37 at 3158 (CabRef0002978); JTX-56 at 11 (CabRef0003470); DTX-2361 at 1 (CabRef0003454); Tr. (Ratain) 327:1-12, 375:5-19.) Accordingly, Plaintiffs were obligated to come forward with evidence to the contrary. *See Ralston Purina Co.*, 772 F.2d at 1573. Plaintiffs did not, however, present evidence to the contrary.

Based on the factual findings set forth above, Defendants have shown by clear and convincing evidence that Claim 11 of the '592 patent is invalid as obvious in view of the prior art. 35 U.S.C. § 103.

(3) Claims 14 and 16

Claim 14 states, "The method according to claim 13, where the prednisone or prednisolone is administered at a dose of 10 mg/day." (JTX-006, column 19, lines 24-25.) Claim 14 depends from Claim 13, which depends from Claim 1, and specifies that the corticoid be prednisone or prednisolone.

Defendants met the procedural burden of establishing a legally sufficient *prima facie* case of invalidity with respect to Claim 14. Defendants asserted that Claim 14 is obvious in view of the Phase III Disclosures, and the docetaxel and taxol labels. The exact dosage of prednisone in the TROPIC trial is not disclosed in the Phase III Disclosures. A POSA, however, would expect the standard prednisone regimen (10 mg/day), as was used with mitoxantrone and with docetaxel, to

be continued in the TROPIC trial. (Tr. (Ratain) 377:6-378:7; JTX-30; JTX-37; JTX-56.) Accordingly, Plaintiffs were obligated to come forward with evidence to the contrary. *See Ralston Purina Co.*, 772 F.2d at 1573. Plaintiffs, however, did not present evidence to the contrary.

Defendants also met the procedural burden of establishing a legally sufficient *prima facie* case of invalidity with respect to Claim 16. Claim 16 states, "The method according to claim 14, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 25 mg/m^2." (JTX-006, column 19, lines 29-31.) Claim 16 depends from Claim 14, and specifies that the cabazitaxel is administered at a dose of 25 mg/m^2. According to Defendants, Claim 16 is obvious in light of the Phase III Disclosures, and the docetaxel and taxol labels. The 25 mg/m^2 dose is explicitly disclosed in the Phase III Disclosures. (Tr. (Ratain) 377:6-16.) Accordingly, Plaintiffs were obligated to come forward with evidence to the contrary. *Ralston Purina Co.*, 772 F.2d at 1573. Plaintiffs, however, did not present evidence to the contrary.

Based on the factual findings set forth above, Defendants have shown by clear and convincing evidence that Claims 14 and 16 of the '592 patent are invalid as obvious in view of the prior art. 35 U.S.C. § 103.

(4) Claims 15 and 26

Claim 15 states, "The method according to claim 14, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m^2." (JTX-006, column 19, lines 26-28.) Claim 15 depends from Claim 14, which depends from Claim 13, which depends from Claim 1. Claim 15 requires the dose of cabazitaxel to be 20 mg/m^2. Claim 26 states, "The method according to Claim 1, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m^2." (JTX-006, column 20, lines 4-6.) Claim 26 depends from Claim 1, and requires the dose of cabazitaxel to be 20 mg/m^2.

Defendants met the procedural burden of establishing a legally sufficient *prima facie* case of invalidity with respect to Claims 15 and 26. According to Defendants, Claims 15 and 26 are obvious in view of Mita, Pivot, and the Taxotere and Taxol labels. Specifically, both Claims 15 and 26 add the same 20 mg/m^2 dose limitation and are obvious for the same reasons as Claims 21 and 30. Accordingly, Plaintiffs were obligated to come forward with evidence to the contrary. *See Ralston Purina Co.*, 772 F.2d at 1573. Plaintiffs, however, did not present evidence to the contrary.

Based on the factual findings set forth above, Defendants have shown by clear and convincing evidence that Claims 15 and 26 of the '592 patent are invalid as obvious in view of the prior art. 35 U.S.C. § 103.

V. CONCLUSION

For the reasons set forth above, the Court finds that: (i) Defendants infringed the '170 patent; (ii) Defendants failed to demonstrate invalidity of the '170 patent by clear and convincing evidence; (iii) Plaintiffs demonstrated by a preponderance of the evidence that Defendants will induce infringement of the '592 patent; and (iv) Defendants demonstrated invalidity of the asserted claims of the '592 patent by clear and convincing evidence. An order consistent with this Opinion will be entered.

s/ Michael A. Shipp
MICHAEL A. SHIPP
UNITED STATES DISTRICT JUDGE

Dated: December 19, 2017