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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN LABORATORIES LIMITED,
Petitioner,

v.

AVENTIS PHARMA S.A.,
Patent Owner.

Case No. IPR2016-00712
Patent No. 8,927,592

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 8,927,592

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I. INTRODUCTION

Mylan Laboratories Limited ("Petitioner") requests review of U.S. Patent No. 8,927,592 to Gupta ("the '592 patent," Ex. 1001), that issued on January 6, 2015, and is currently assigned to Aventis Pharma S.A. ("Patent Owner"). This Petition demonstrates a reasonable likelihood that claims 1-5 and 7-30 of the '592 patent are unpatentable for failing to distinguish over prior art.

Independent claim 1 is to a method of treatment that requires:

- administering 20 to 25 mg/m^2 of cabazitaxel, or its hydrate or solvate;
- in combination with a corticoid;
- to a patient with prostate cancer; and
- that the cancer progressed during or after treatment with docetaxel (Taxotere®).

The claimed method administers a known drug, in a known dosage range, in a known combination, with known activity against a known indication, to patients with that indication. Independent claim 27 specifies metastatic "castration resistant or hormone refractory" prostate cancer, and a prednisone or prednisolone corticoid.

The claimed method was published more than one year before the earliest alleged priority date of the '592 patent. As just one example, Winquist discloses an ongoing Phase III clinical study ("the TROPIC study") in which 25 mg/m^2 of cabazitaxel (referenced as XRP-6258) was administered to patients in combination with prednisone (a corticoid) for treating hormone-refractory (castration-resistant) metastatic prostate cancer ("mCRPC") previously treated with docetaxel. Ex. 1009.

As another example, the TROPIC Listing describes the same TROPIC study

as Winquist. The TROPIC Listing discloses that the TROPIC study had been ongoing for almost two years (since December 2006). In order to participate in the study, the TROPIC Listing discloses that the included mCRPC patients, who were all previously treated with docetaxel, must have "[d]ocumented progression of disease," including "rising PSA[prostate-specific antigen] levels or appearance of [a] new lesion." Ex. 1008. Thus, the TROPIC Listing confirms that the 25 mg/m^2 dose of cabazitaxel administered to mCRPC patients in the TROPIC Study, as disclosed in Winquist, was administered to patients whose mCRPC had progressed during or after treatment with docetaxel. In view of Winquist and the TROPIC Listing, claims 1-2, 5, 7-9, 12-13, 17-20, 22-25, 27-29 of the '592 patent are each obvious. The remaining features of claims 3-4, 10-11, 14-16, 21, 26, and 30 are minor, obvious limitations in view of the prior art.

In addition, Pivot describes a Phase II study of cabazitaxel, in which doses of 20-25 mg/m^2 of cabazitaxel were administered to patients with taxane-resistant breast cancer (two-thirds of which were docetaxel-resistant). In view of Pivot and Winquist, claims 1-2, 5, 7-9, 12-13, 17-30 of the '592 patent are each obvious. The remaining features of claims 3-4, 10-11, 14-16 are minor, obvious limitations in view of the prior art.

Despite the prior art, Patent Owner is attempting through the '592 patent to monopolize a previously-disclosed therapeutic method based on the subsequent disclosure of Phase III clinical data collected using that method. Patent Owner has stated that there was no "unexpected property" or "unexpected benefit here," and there is none. But even if the Phase III results had been surprising and unexpected

(they were not), efficacy of the method is inherent in the method itself, and clinical data from a known process directed to a known purpose is not patentable.

A. Brief Overview of the '592 Patent

The '592 patent is entitled "Antitumoral Use of Cabazitaxel," and has an earliest claimed priority date of October 29, 2009. Application No. 13/456,720 ("the '720 application") was filed on April 26, 2012, and issued on January 6, 2015, as U.S. Patent No. 8,927,592. The '720 application is a continuation of International Application No. PCT/IB2010/054866, filed on October 27, 2010, and claims priority to seven different U.S. Provisional Patent Applications, ultimately to 61/256,160 ("the '160 application," Ex. 1005), filed October 29, 2009.

The '592 patent is directed to treating prostate cancer by administering cabazitaxel. For example, claim 1 is to a method for treating a patient with prostate cancer that has progressed during or after treatment with docetaxel, comprising administering cabazitaxel at a dose of 20 to 25 mg/m^2, in combination with a corticoid. Claim 2 recites that the prostate cancer is an advanced metastatic disease, and claims 17 and 20 recite castration resistant or hormone-refractory prostate cancer. Dependent claims 13 and 24 recite that the corticoid is prednisone or prednisolone, and claim 14 recites the prednisone or prednisolone is administered at a dose of 10 mg/day. Independent claim 27 recites a method for increasing survival of a patient with castration resistant or hormone refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel, comprising administering cabazitaxel at a dose of 20 to 25 mg/m^2, in combination with prednisone or prednisolone.

Dependent claims 12, 15, 16, 18, 21, 22, 24, 26, 28 and 30 specify that cabazitaxel is administered at a dose of either 20 mg/m^2 or 25 mg/m^2. Dependent claims 5, 19, 23, 25, and 29 recite that the administration of cabazitaxel is repeated in 3-weekly cycles. Dependent claims 3-4 recite that the cabazitaxel is in the form of an acetone solvate. Dependent claim 10 recites monitoring blood counts and neutrophil levels in the patient, and dependent claim 11 recites discontinuing treatment if neutrophils are below a specified amount.

Dependent claims 7-9 recite that cabazitaxel is administered in an amount to provide specified pharmacokinetic parameters. Claims 7-9 of the '592 patent are not entitled to the priority date of October 29, 2009, or to the benefit of provisional application 61/293,903 ("the '903 application," Ex. 1006), filed January 11, 2010. The pharmacokinetic parameters of claims 7-9 were not disclosed in either of these provisional applications, nor could they be deduced from the disclosures provided therein. Ex. 1002, ¶ 13. The '834 application (Ex. 1007), filed June 17, 2010, is the earliest filed provisional containing written support for distributions of pharmacokinetic parameters (AUC, C_{max}, and plasma clearance), as recited in claims 7-9. Ex. 1002, ¶¶ 11-13. Accordingly, the relevant timeframe for assessing validity of claims 7-9 is prior to June 17, 2010. Ex. 1002, ¶ 14.

B. Brief Overview of the Prosecution History

During prosecution of the '720 application, claims to treating prostate cancer by administering cabazitaxel and prednisone were rejected over Mita *et al.* (Ex. 1012) and Tannock *et al.* (Ex. 1013). Ex. 1004 at 01874, 02224. Mita discloses Phase I data evaluating safe dose ranges for administering cabazitaxel to patients

with advanced solid tumors, including breast and prostate cancer. Ex. 1012 at 723. Mita also discloses pharmacokinetic properties of cabazitaxel. *Id.* Mita does not disclose Phase II clinical data, and does not state that it involved administering cabazitaxel to patients with mCRPC that had progressed during or after treatment with docetaxel. Ex. 1012. Tannock discloses co-administering docetaxel, of which cabazitaxel is a close analogue, with prednisone. Ex. 1013.

Subsequently the claims were rejected as both anticipated by Beardsley *et al.* (Ex. 1022), and as obvious over Beardsley, Mita and Tannock. Ex. 1004 at 00252-68. Beardsley reviews treatments for castration- (or hormone-) resistant prostate cancer, stating: "The current first-line standard of care for patients with symptomatic or progressive disease is docetaxel-based chemotherapy." Ex. 1022. Beardsley noted a variety of second-line treatments, *i.e.*, treatments for patients with disease progression after or during docetaxel chemotherapy. *See id.*; Ex. 1002, ¶ 27. Beardsley reported that administering cabazitaxel to patients with docetaxel-resistant metastatic breast cancer resulted in an objective response rate of 14%, and that based on this result, a Phase III study had been initiated among prostate cancer patients with mCRPC previously treated with docetaxel. Ex. 1022 at 163. Beardsley does not disclose the dose of cabazitaxel being administered in the Phase III trial. *Id.*

The applicant held an in-person interview with the examiner on July 10, 2014. Ex. 1004 at 00143, 00230. According to the interview summary, the examiner agreed the claims would be allowable if they were amended "to recite (1) treatment of prostate cancer in patients ***who had progressed during or after***

docetaxel treatment and (2) administering a dose of ***20 to 25 mg/m^2*** ***cabazitaxel*** . . . in combination with a corticoid." *Id.* (emphases added).

On July 16, 2014, applicant submitted an amendment making the agreed changes from the interview (*id.* at 137-138, 140), accompanied by the §1.132 declaration of Dr. Sartor (*id*. at 0164-92). In remarks, applicant repeatedly argued that the absence of the 20 to 25 mg/m^2 dosage range in the prior art was important evidence rebutting the examiner's rejections. *Id.* at 0145 ("Importantly, the doses of cabazitaxel and prednisone are not disclosed in Beardsley. . . . Beardsley does not describe *any* dose of cabazitaxel, let alone an *effective* amount of cabazitaxel." (emphasis in original)); *id.* at 0148. A Notice of Allowance ensued. *Id*. at 0091-94.

C. Brief Overview of the Scope and Content of the Prior Art

In obviousness cases, *Graham v. John Deere Co. of Kansas City*, requires an evaluation of any differences between the claimed subject matter and the asserted prior art. 383 U.S. 1, 17-18 (1966). As noted in *KSR Int'l Co. v. Teleflex Inc.*, it is not necessary to have precise teachings in the art directed to the specific subject matter claimed because inferences and creative steps that a person of ordinary skill in the art would employ can be taken into account. 550 U.S. 398, 418 (2007).

i. Winquist et al., Canadian J. of Urology, 15(1), 2008 (Ex. 1009)

Winquist provides a listing for the Phase III TROPIC study: "A randomized, open-label multicentre study of XRP-6258 [cabazitaxel] at 25 mg/m^2 in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone-refractory metastatic prostate cancer previously treated with a Taxotere [docetaxel]-containing

regimen." Ex. 1009 at 3948. The study included 720 patients with "[h]ormone-refractory prostate cancer previously treated with docetaxel," and "overall survival" was the primary end-point. *Id*. Winquist does not explicitly teach cabazitaxel as an acetone solvate, its pharmacokinetic parameters, or monitoring neutrophils. Winquist is prior art to the claims under 35 U.S.C. § 102(b).

ii. <u>The TROPIC Listing (Ex. 1008)</u>

A second listing for the Phase III TROPIC study (Ex. 1008; hereinafter "the TROPIC Listing") was published in the ClinicalTrials.gov database of the National Library of Medicine, and archived by The Internet Archive on October 23, 2008 (as authenticated by the affidavit of C. Butler, Ex. 1026). The TROPIC Listing discloses that the Phase III TROPIC study had been ongoing for nearly two years (since December 2006), and was "a randomized, open-label, multi-center study comparing the safety and efficacy of XRP6258 [cabazitaxel] plus prednisone to mitoxantrone plus prednisone in the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere [docetaxel]-containing regimen." Ex. 1008 at 0001-0002. The TROPIC listing also states that cabazitaxel is to be administered every three weeks and that patients must have a "[d]ocumented progression of disease (demonstrating at least one visceral or soft tissue metastatic lesion, including a new lesion) . . . [or] rising PSA levels or appearance of a new lesion." *Id*. at 0001-02. The primary objective of the TROPIC study was overall survival. *Id*. at 0001. The TROPIC Listing does not explicitly describe acetone solvate of cabazitaxel, administration doses and the resulting pharmacokinetic parameters, or monitoring neutrophil cell counts. The TROPIC

Listing is prior art under 35 U.S.C. § 102(b).

iii. Pivot et al., Annals of Oncology 19:1547-1552, 2008 (Ex. 1010)

Pivot discloses a Phase II clinical study administering cabazitaxel every three weeks to patients with metastatic breast cancer, including patients previously treated with docetaxel. Ex. 1010 at 1547-49. Pivot discloses administering 20 and 25 mg/m^2 of cabazitaxel and concludes that the safety profile at these doses was "very favorable" compared to the marketed taxanes (*i.e.*, paclitaxel and docetaxel). *Id*. at 1548, 1551. Pivot observed a 14% objective response rate among cabazitaxel-treated metastatic breast cancer patients, and concluded that cabazitaxel "appears to be active in docetaxel- or paclitaxel-resistant breast cancer, even when the most stringent criterion of resistance (P[rogressive]D[isease] on therapy) was used." *Id.* at 1551. Pivot teaches that tumors with high expression of P-glycoprotein were resistant to taxanes, and that cabazitaxel was selected for its low affinity for P-glycoprotein, which was encoded by the multidrug resistant gene *ABCB1*. *Id*. at 1547-48. Pivot also teaches that cabazitaxel was known to be effective against docetaxel-resistant cancer cells. *Id.* Pivot does not teach cabazitaxel as an acetone solvate, describe treatment of prostate cancer with cabazitaxel, or expressly teach its pharmacokinetic parameters. Pivot is prior art to the claims under 35 U.S.C. § 102(b).

iv. U.S. Patent No. 7,241,907 to Didier et al. ("Didier," Ex. 1011)

Didier teaches an acetone solvate of cabazitaxel and its preparation from an aqueous/acetone solution. Ex. 1011, abstract. Didier further discloses the solvate containing from about 5% to about 7% by weight of acetone, including specific

percentages within this range. *Id*. at 2:39-42 and claim 2. Didier is prior art under 35 U.S.C. § 102(b).

v. Mita et al., Clin. Cancer Res., 15(2), 2009 (Ex. 1012)

Mita describes a Phase I pharmacokinetic study of cabazitaxel "designed primarily to determine the maximum tolerated dose and the dose-limiting toxicity of XRP6258 [cabazitaxel] given as a 1-hour i.v. infusion." Ex. 1012 at 724. Mita discloses administering cabazitaxel at several doses, including 20 and 25 mg/m^2, and reports distributions of pharmacokinetic parameters obtained at these doses, *e.g*., area under the curve (AUC), maximum plasma concentration (C_{max}) and clearance (CL). *Id*. at 729. Mita does not teach cabazitaxel as an acetone solvate. For claims 7-9, Mita is prior art under 35 U.S.C. § 102(b).

vi. Tannock et al., N. Engl. J. Med. 351, 2004, 1502-1512 (Ex. 1013)

Tannock describes a Phase III clinical study in which patients with metastatic hormone-refractory prostate cancer were treated in 3-week cycles with docetaxel, with prednisone given at a dose of 10 mg/day via two 5 mg administrations. Ex. 1013 at 1502-03. Tannock concluded, "[w]hen given with prednisone, treatment with docetaxel every three weeks led to superior survival and improved rates of response in terms of pain, serum PSA level and quality of life." *Id*., at 1502. Tannock teaches determining neutrophil counts and reducing or delaying treatment in patients with counts below 1,500/mm^3. *Id*., at 1504. Tannock is §102(b) prior art.

D. Brief Overview of the Level of Skill in the Art

A person of ordinary skill in the art as of October 29, 2009 (or June 17, 2010

as to claims 7-9 of the '592 patent), would be an oncologist, would hold a medical degree (*e.g.*, a D.O. or an M.D.), and would have experience treating patients with prostate cancer by administering chemotherapeutic drugs. Ex. 1002, ¶ 40. The skilled artisan would likely have some combination of the following skills and experience: (a) treatment of metastatic prostate cancer by administering taxanes, including docetaxel; (b) treatment of docetaxel-resistant prostate cancer; (c) treatment of castration resistant prostate cancer; and (d) the ability to understand publications in the field, including those discussed herein. *Id.* In particular, the means of administering taxane drugs and prednisone to prostate cancer patients would be a routine matter for a person of ordinary skill in the art. *Id.*

Submitted concurrent with this petition is a declaration from Dr. Rahul Seth. Dr. Seth is an Assistant Professor of Medicine at SUNY Upstate Medical University, where he has been a member of the faculty since 2009. Dr. Seth is also a practicing oncologist, with his practice including work at the prostate cancer program at Upstate University Hospital in Syracuse, NY. Ex. 1002, ¶ 1; *see also*, Ex. 1003. He received a Doctor of Osteopathy degree from the New York College of Osteopathic Medicine in 1999, and has been board-certified in oncology since 2006. Ex. 1002, ¶ 2; *see also*, Ex. 1003. Dr. Seth completed his residency in internal medicine in 2002, and completed a fellowship in hematology and oncology in 2005, both at Stony Brook University Hospital. Ex. 1002, ¶ 1; *see also*, Ex. 1003. Prior to medical training, Dr. Seth received a B.S. in Biology from Carnegie Mellon University in 1991 and a M.S. in Biochemistry and Toxicology from Brown University in 1995. Ex. 1002, ¶ 2; *see also*, Ex. 1003.

Dr. Seth's research and clinical practice is focused on urological oncology and gastrointestinal cancers. Ex. 1002, ¶ 3; *see also*, Ex. 1003. He has been administering taxanes for the treatment of prostate cancer since 2002, and has treated over 60 patients with metastatic prostate cancer using active chemotherapy, often with taxane drugs. Ex. 1002, ¶ 3; *see also*, Ex. 1003. Dr. Seth has also been actively involved in a number of clinical studies, including Phase III studies directed to treating cancer using taxane drugs. Ex. 1002, ¶ 3; *see also*, Ex. 1003.

Dr. Seth is well qualified as an expert, possessing the necessary clinical expertise and other specialized knowledge, as of October 29, 2009 and as of June 17, 2010, to assist in an understanding of the evidence presented herein, as well as possessing the expertise necessary to determine and explain the level of ordinary skill in the art during the relevant time frame. *See* Ex. 1002, ¶¶ 1-4; Ex. 1003.

II. GROUNDS FOR STANDING

Petitioner certifies that, under 37 C.F.R. § 42.104(a), the '592 patent is available for *Inter Partes* Review, and Petitioner is not barred or estopped from requesting *Inter Partes* Review of the '592 patent on the grounds identified.

III. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

The following real parties-in-interest are identified: Mylan Laboratories Limited, which is the Petitioner in this matter and which is a wholly owned subsidiary of Mylan Inc.; Mylan Pharmaceuticals Inc., which is a wholly owned subsidiary of Mylan Inc.; Mylan Inc., which is an indirectly wholly owned subsidiary of Mylan N.V.; and, Mylan N.V.

Related Matters (37 C.F.R. § 42.8(b)(2)):

Petitioner has filed IPR2016-00627 for a patent directed to cabazitaxel, U.S. Patent No. 6,847,170. The '592 patent issued from application 13/456,720 and is a continuation of PCT/IB2010/054866, which claims priority to U.S. provisional applications 61/256,160 (Ex. 1005, filed October 29, 2009); 61/293,903 (Ex. 1006, filed January 11, 2010); 61/355,834 (Ex. 1007, filed June 17, 2010); 61/355,888, filed June 17, 2010; 61/369,929, filed August 2, 2010; 61/383,933, filed September 17, 2010; and 61/389,969, filed October 5, 2010. Petitioner is aware of pending continuations 14/575,566 and 14/575,578.

Petitioner and other entities have been involved in litigation over the '592 patent in the action styled *Sanofi-Aventis U.S. LLC et al. v. Mylan Laboratories Limited*, C. A. No. 15-03392 (MAS)(LHG), filed in the District of New Jersey (Ex. 1014). A waiver of service of the complaint asserting the '592 patent against Petitioner was filed in court no earlier than June 2, 2015.

Petitioner is aware of other pending actions involving the '592 patent: *Sanofi-Aventis U.S. LLC et al. v. Apotex Corp. et al.*, C. A. No. 15-01835; *Sanofi-Aventis U.S. LLC et al. v. Breckenridge Pharmaceutical, Inc.*, C. A. No. 15-01836; *Sanofi-Aventis U.S. LLC et al. v. Accord Healthcare, Inc.*, C. A. No. 15-02520; *Sanofi-Aventis U.S. LLC et al. v. BPI Labs, LLC et al.*, C. A. No. 15-02521; *Sanofi-Aventis U.S. LLC et al. v. Dr. Reddy Laboratories, Inc. et al.*, C. A. No. 15-02522; *Sanofi-Aventis U.S. LLC et al. v. Glenmark Generics Inc. et al.,* C. A. No. 15-02523; *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 15-02631; *Sanofi-Aventis U.S. LLC et al. v. Actavis LLC et al.*, C. A. No. 15-03107.

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

Lead Counsel: Steven W. Parmelee (Reg. No. 31,990)

Back-Up Counsel: Michael T. Rosato (Reg. No. 52,182)

Back-Up Counsel: Jad A. Mills (Reg. No. 63,344)

Service Information – 37 C.F.R. § 42.8(b)(4).

Petitioner hereby consents to electronic service.

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IV. STATEMENT OF THE PRECISE RELIEF REQUESTED

Petitioner requests review of claims 1-5 and 7-30 of the '592 patent under 35 U.S.C. § 311 and AIA § 6 on the grounds that they are unpatentable and invalid, and should be canceled, as follows:

Ground	Claims	Obvious under §103 over
1	1, 2, 5, 7-9, 12, 13, 17-20, 22-25, 27-29	Winquist and the TROPIC Listing
2	3, 4	Winquist, the TROPIC Listing, and Didier
3	7-9	Winquist, the TROPIC Listing, and Mita
4	10, 11, 14, 16	Winquist, the TROPIC Listing, and Tannock
5	21, 26, 30	Winquist, the TROPIC Listing, and Pivot
6	15	Winquist, the TROPIC Listing, Pivot, and Tannock
7	1, 2, 5, 7-9, 12, 13, 17-30	Winquist and Pivot
8	3, 4	Winquist, Pivot, and Didier

9	7-9	Winquist, Pivot, and Mita
10	10, 11, 14-16	Winquist, Pivot, and Tannock

V. STATEMENT OF NON-REDUNDANCY

Each of the ten Grounds raised in this Petition is meaningfully distinct:

Ground 1 presents obviousness of claims 1, 2, 5, 7-9, 12, 13, 17-20, 22-25, and 27-29, based on a combination of Winquist and the TROPIC Listing. Winquist and the TROPIC Listing each describe a method for treating mCRPC previously treated with docetaxel by administering cabazitaxel and prednisone. Winquist expressly discloses a dose of 25 mg/m^2. The TROPIC Listing details progression of the cancer during or after docetaxel treatment.

Grounds 2-6 each establish the obviousness of certain dependent claims, where additional prior art is applied to claim elements that are minor and well-known limitations in view of the prior art.

Ground 7 presents obviousness of claims 1, 2, 5, 7-9, 12, 13, and 17-30 based on a combination of Winquist and Pivot. This Ground is materially different from Ground 1 in that Pivot discloses treating docetaxel-resistant breast cancer by starting at a dose of 20 mg/m^2 and increasing the dose to 25 mg/m^2 if well tolerated, an aspect not expressly taught by the references in Ground 1. Winquist describes treating mCRPC previously treated with docetaxel by administering cabazitaxel at 25 mg/m^2 together with prednisone. Grounds 8-10 address other dependent claims that recite minor and well known features of the prior art.

VI. CLAIM CONSTRUCTION

In an *inter partes* review, a claim in an unexpired patent is given its broadest

reasonable construction in light of the specification. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1275-1280 (Fed. Cir. 2015), *cert. granted*, *Cuozzo Speed Techs., LLC v. Lee*, 2016 U.S. LEXIS 632 (U.S. Jan. 15, 2016) (No. 15-446). Claims terms are also "generally given their ordinary and customary meaning," i.e., the meaning the term would have to a person of ordinary skill in the art at the time of the invention in view of the specification. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Under either legal standard, there is a reasonable likelihood that Petitioner will prevail with respect to the challenged claims. Claim terms that warrant construction are discussed below.

A. "dose"

The term "dose" appears, *e.g.*, in claim 1 of the '592 patent, but is not defined in the patent. The plain and ordinary meaning of the term "dose" is the total amount of drug administered during an administration cycle. Ex. 1002, ¶ 42.

B. "prostate cancer that has progressed"

Claims 1 and 27 refer to "prostate cancer that has progressed." The '592 patent states that in Example 1, "progression" was evaluated as "at least [a] 20% increase in the sum of the largest diameter of the lesion or appearance of one or more new lesions" or as "either an increase of the PSA, or of the tumour, or of the pain." Ex. 1001 at 11:10-25. The Patent Owner has previously agreed that "prostate cancer that has progressed" includes "prostate cancer that has worsened." Ex. 1031 at 00006. Accordingly, "prostate cancer that has progressed" includes prostate cancer that exhibits increasing PSA, tumor size, or pain; new lesions; or worsening. Ex. 1002, ¶ 48.

C. "advanced metastatic disease"

The term "advanced metastatic disease" is not defined in the '592 patent. However, in the context of prostate cancer, "advanced metastatic disease" would be understood by a skilled artisan to include a prostate cancer that has widely metastasized beyond the prostate, the surrounding tissue, and the pelvic lymph nodes. *See, e.g*. Ex. 1030 at S11; Ex. 1002, ¶ 49. This includes metastasis into the visceral organs, such as the heart, lungs, liver, pancreas, or intestines. *Id.* A skilled artisan would also understand a prostate cancer that is an advanced metastatic disease to include a prostate cancer that has PSA relapse (rising PSA levels) following first-line treatment, for example, following treatment with docetaxel. *See, e.g*. Ex. 1030 at S11; Ex. 1002, ¶ 50. Further, Patent Owner has asserted in litigation that "advanced metastatic disease" includes "Castration resistant (hormone refractory), metastatic prostate cancer." Ex. 1031 at 00018.

Accordingly, when used in the context of prostate cancer, the broadest reasonable interpretation of the term "advanced metastatic disease" includes each of prostate cancer exhibiting at least one visceral or soft tissue metastatic lesion, prostate cancer exhibiting rising PSA levels following treatment with docetaxel, and castration-resistant or hormone-refractory metastatic prostate cancer.

D. "castration-resistant" and "hormone-refractory"

"Castration resistant prostate cancer, as used herein, is synonymous with hormone-refractory prostate cancer." Ex. 1001, col. 4, ll. 4-5.

E. "C_{max}"

The term "C_{max}" appears in claim 8 of the '592 patent. C_{max} is expressed in

claim 8 of the '592 patent in units of "ng·h/mL." But the specification of the '592 patent refers to C_{max} in units of "ng/mL." Ex. 1001, col. 18, ll. 36-40. The Patent Owner has previously agreed that "ng·h/mL" in claim 8 should read "ng/mL." Ex. 1031 at 00006. Thus, in light of the specification of the '592 patent, the broadest reasonable interpretation of a "C_{max} of about 226 ng·h/mL" includes a "C_{max} of about 226 ng/mL." Ex. 1002, ¶53- 54.

F. "CV"

The term "CV" appears in claims 7-9 of the '592 patent. "CV" is an acronym for "coefficient of variation," a statistical term defined as the standard deviation of a distribution divided by its average. Ex. 1016 at 00005; Ex. 1002, ¶ 57. The plain and ordinary meaning of "X (CV Y%)," where X is a value including a unit of measure, and Y is expressed as a percent, is a distribution of values, for which any value from a lower bound of (X – X×Y÷100) to an upper bound of (X + X×Y÷100) is within one standard deviation of the average. *Id.*

G. "A method for treating"

The preamble phrase "[a] method for treating" in claim 1 is not limiting. "[A]s a general rule preamble language is not treated as limiting." *Aspex Eyewear, Inc. v. Marchon Eyewear, Inc.*, 672 F.3d 1335, 1347 (Fed. Cir. 2012). A preamble is "not limiting 'where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention.'" *Braintree Labs., Inc. v. Novel Labs., Inc.*, 749 F.3d 1349, 1357 (Fed. Cir. 2014) (quoting *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997)). In some circumstances, a portion of a preamble may limit the scope of the claims, though

another portion of the same preamble does not. *See, e.g.*, *TomTom, Inc. v. Adolph*, 790 F.3d 1315, 1322-24 (Fed. Cir. 2015).

Here, the preamble language "[a] method for treating" is used only to state an intended use for the invention and is not necessary to give meaning or "breathe life into the claim." *See Aspex Eyewear*, 672 F.3d at 1347. Although the adjacent language ("a patient with prostate cancer . . . ") provides antecedent basis for the term "said patient," the phrase "for treating" is not required for meaning.

If it were limiting, the plain and ordinary meaning of the phrase "[a] method for treating a patient" would include "a method intended to benefit a patient." The plain meaning of "treating a patient" does not require causing a therapeutic benefit. *See, e.g.*, *Schering Corp. v. Mylan Pharms., Inc.*, 09-cv-6383, 2011 WL 2446563, at *2, *5 (D.N.J. June 15, 2011) ("To treat a disease does not imply that the progression of the disease will actually be slowed, arrested, or reversed . . . ."). Indeed, treating a patient includes treatments that provide no therapeutic benefits, such as palliative treatments, and treatments for which there is great uncertainty as to whether the intended benefit will result, such as in experimental treatments and even in FDA approved treatments. Ex. 1002, ¶¶ 43-45. If "treating" is limiting, it should be construed with its plain meaning, as "intended to benefit a patient."

The specification of the '592 patent is consistent with this plain meaning. For example, claims 1 and 27 are directed to methods for "treating" a patient with "prostate cancer that has progressed during or after ***treatment*** with docetaxel." Ex. 1001 at 18-20. These terms should be construed consistently. *See z4 Techs., Inc. v. Microsoft Corp.*, 507 F.3d 1340, 1348 (Fed. Cir. 2007). But the '592 patent

indicates that docetaxel "treatment" was not successful, specifically declaring that, in at least some cases, "the patient showed progression of their disease . . . ***during docetaxel treatment***." *See e.g.*, Ex. 1001 at 5:64-67, (emphasis added); *see also id.* at 10:44-45 (clinical study population was limited to patients "who had progress[ed] during or after docetaxel treatment"); *id.* at 11:39-42 ([One-]third of patients . . . had ***progressed during docetaxel therapy***.").

That "treating" does not require actual therapeutic results is also confirmed by the prosecution history. For example, when discussing a clinical study in a prior art reference, the Patent Owner stated that "no antitumor activity was seen in the majority of the patients ***treated***." Ex. 1004 at 00147, 00286 (emphasis added). As another example, the Sartor declaration stated that mitoxantrone "had been previously shown ***not*** to improve survival." (Ex. 1004 at 00184 (emphasis added)), yet the '592 patent refers to mitoxantrone as a "reference treatment." Ex. 1001 at 1:60-62. Accordingly, the specification and prosecution history of the '592 patent confirm that the plain meaning of the term "treating" includes "intending to benefit a patient," even if the intended benefit does not result.

H. "A method of increasing the survival of"

The preamble phrase "[a] method of increasing the survival of" in claim 27 is not limiting, for the same reasons discussed above with regard to the term "[a] method for treating." If it were limiting, the broadest reasonable interpretation of the phrase "[a] method of increasing the survival of a patient" would include "a method intended to increase the survival of a patient." Indeed, as shown in Fig. 1 of the '592 patent, illustrating "curves of the overall survival in a cabazitaxel

study" (Ex. 1001 at col. 3, ll. 36-37), more patients treated with cabazitaxel died in the first 3 months of treatment than patients treated with mitoxantrone. Thus, although the administration of cabazitaxel to each patient may be ***intended*** to increase his survival, patients treated with cabazitaxel actually showed a ***decrease*** in survival during the first three months of treatment. Accordingly, construing the preamble phrase "[a] method of increasing survival of a patient" to require that the method actually result in an increase in survival would contradict the specification.

Moreover, a construction of this phrase that required an increase in survival to result from performance of the method would be nonsensical. As explained by Dr. Seth, in the context of prostate cancer, it is not known at the time of administering a drug whether that drug will result in any increase in survival of the patient, though such a benefit may be intended and be the motivation for administering even an experimental treatment. Ex. 1002, ¶¶ 43-47. Construing the preamble phrase to require that statistically significant results be previously reported from Phase III human clinical studies, would contradict the '592 patent's definition of the claim term "patient," which extends beyond clinical human uses: "'Patient,' as used herein, includes both human and animals." Ex. 1001 at 4:6-7. Thus, the phrase "[a] method of increasing the survival of a patient" includes "a method intended to increase the survival of a patient."

VII. BACKGROUND KNOWLEDGE IN THE ART PRIOR TO OCTOBER 29, 2009

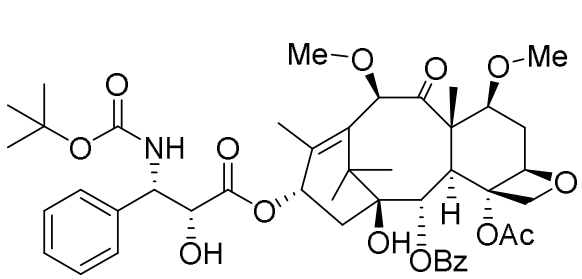
The following background publications are discussed in the context of the knowledge and perspective of one of ordinary skill in the relevant art. This background provides a factual basis for the discussion about what one of ordinary

skill would have known at the time of the invention, assumed for the purposes of this Petition to be the earliest alleged priority date, and documents the knowledge that skilled artisans would bring to bear in reading the prior art. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359 (Fed. Cir. 2015). This knowledge assists in understanding why a skilled artisan would have been motivated to combine or modify the references asserted in the grounds of this petition to arrive at the claimed invention. As *KSR* established, this knowledge is part of the store of public knowledge that must be consulted when considering obviousness. *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013).

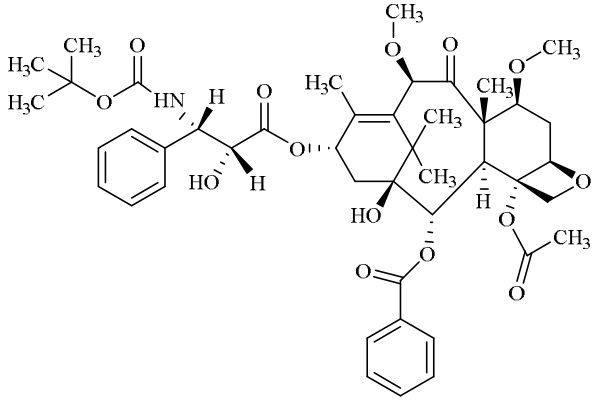
Prior to October 29, 2009, the use of taxanes (*e.g.*, docetaxel) to treat cancer was well known in the art. *See* Ex. 1002, ¶¶ 59-60, 63 discussing Abrams (Ex. 1017), Kelland (Ex. 1018), and Verweij (Ex. 1019). Docetaxel received FDA approval first as a treatment for breast cancer, then later as a treatment for mCRPC. Ex. 1002 at ¶ 69, citing Attard (Ex. 1021); *id.* at ¶ 74, citing Hopkins (Ex. 1032). Compounds effective against one cancer are frequently effective against the other, and the cancers share much in common, including genetic links and hormonal-induced growth. Ex. 1002 ¶¶ 74-76.

Cabazitaxel, a close structural analogue of docetaxel, was also referred to in the art as XRP-6258 and was a known taxoid compound having activity in cancer cell lines that were resistant to paclitaxel and docetaxel. *E.g.*, Galletti*, et al.*, *"Paclitaxel And Docetaxel Resistance: Molecular Mechanisms and Development of New Generation Taxanes," CHEMMEDCHEM*, *2*, 2007, 920 (Ex. 1020), at 930 (Table 1), 933; Ex. 1002, ¶ 64. Cabazitaxel was known to have the same

mechanism of action as docetaxel (at the taxane-binding site of beta-tubulin), which was known to be effective in both breast cancer and mCRPC. *See* Ex. 1002, ¶¶ 66-69, discussing Attard. The structure of XRP-6258 disclosed in Galletti is shown below (left), adjacent to the identical structure for cabazitaxel disclosed in the '592 patent (2:38-57):



XRP6258
(RPR-116258A)



Cabazitaxel was also known to have shown efficacy in patients with docetaxel-resistant, castration-resistant prostate cancer.

> **One of the major limitations of the currently used taxanes is the development of drug resistance** . . . . P-glycoprotein (P-gp) efflux pump . . . [is] a major mechanism of . . . resistance to taxanes in cell lines . . . . XRP6258 (RPR-116258A). . . [has] minimal affinity for P-gp . . . . XRP6258 was investigated in phase I studies in a three-weekly schedule and the maximum tolerated dose (MTD) was reached at 20 mg/m^2. **Two objective responses, both in CRPC [castration resistant prostate cancer], were seen. One of the patients was docetaxel refractory.** Anti-tumour activity was reported in tumours classically resistant to taxanes, such as osteosarcoma, and in tumours with acquired resistance following prior treatment with taxanes. This indicates that this agent may overcome some forms of paclitaxel tumour resistance.

See Attard *et al*., *Update on Tubulin-Binding Agents*, PATHOLOGIE BIOLOGIE, *54*, 2006, 72 ("Attard," Ex. 1021), at 74-75 & Table 3 (emphases added; citations removed). According to the RECIST guidelines, an objective response means a reduction of at least 30% in tumor diameter, corresponding to more than a 50% reduction in volume. Ex. 1002, ¶ 69. Thus, it was known in the art that cabazitaxel had shown efficacy in treating patients with docetaxel-resistant prostate cancer. *Id*; Ex. 1002, ¶¶ 66-69.

The efficacy of cabazitaxel against docetaxel-resistant cancers was validated by both Phase I and Phase II clinical studies, which served as motivation for a Phase III study against prostate cancer that was underway well prior to October 29, 2009, as is disclosed by Beardsley*, et al., "Systemic Therapy after First-Line Docetaxel in Metastatic Castration-Resistant Prostate Cancer," CURR. OPIN. SUPPORT. PALLIAT. CARE*, *2*, 2008, 161 ("Beardsley," Ex. 1022):

> A phase II study of XRP6258 was conducted in patients with docetaxel refractory metastatic breast cancer . . . . **[G]iven its activity in the docetaxel refractory setting described above, the agent is currently being investigated in a phase III** multicenter, randomized superiority trial comparing 3-weekly XRP6258 with prednisone to mitoxantrone with prednisone in patients with castrate resistant metastatic prostate cancer previously treated with docetaxel-containing treatment.

See Ex. 1022 at 163 (emphasis added). Thus, Beardsley articulates the understanding in the field that the success of cabazitaxel against docetaxel-resistant metastatic breast cancer provided motivation for the Phase III clinical study against docetaxel-resistant mCRPC. The use of cabazitaxel in combination with

prednisone to treat docetaxel-resistant mCRPC was thus known in the art well prior to October 29, 2009. *Id.*; Ex. 1002, ¶¶ 70-72.

Several important aspects of treating prostate cancer with taxanes were also known in the art well before October 29, 2009. For example, as described in the Taxotere Label, FDA, 1996 ("Taxotere Label," Ex. 1024), it was well known that when administering docetaxel, a close structural analogue of cabazitaxel, blood cell counts must be monitored to avoid neutropenia, and treatment should be discontinued if neutrophil counts are below 1,500 cells/mm^3. Ex. 1024 at 2, ll. 19-21; Ex. 1002, ¶¶ 61-62. It was also well known that taxanes such as docetaxel are to be administered in combination with corticoids such as prednisone: "For hormone-refractory metastatic prostate cancer . . . Prednisone 5 mg orally twice daily is administered continuously." Ex. 1024 at 4, l. 20.

The use and benefits of acetone solvates of pharmaceutical compounds were also well known in the art prior to October 29, 2009, as described, *e.g.*, by Liu, WATER INSOLUBLE DRUG FORMULATION, Second Edition, 2008 ("Liu," Ex. 1025). With respect to taxanes, which were known in the art to be water-insoluble, Liu further states: "Paclitaxel is highly lipophilic and insoluble in water . . . It has to be in a soluble form in order to prepare an intravenous formulation." *Id.* at 267. Liu provides a short list of solvents that can be used to form pharmaceutical solvates, including acetone. *Id.* at 531. Thus the use of acetone solvates to improve water solubility of water-insoluble drugs, such as taxanes, was known in the art prior to October 29, 2009. Ex. 1002, ¶¶ 79-80.

VIII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Grounds Asserting Winquist and the Tropic Listing.

i. [Ground 1] Claims 1-2, 5, 7-9, 12-13, 17-20, 22-25, and 27-29: Obvious over Winquist and the TROPIC Listing.

1. Claim 1

Claim 1 recites:

> A method for treating a patient with prostate cancer that has progressed during or after treatment with docetaxel, comprising administering to said patient a dose of 20 to 25 mg/m^2 of cabazitaxel, or a hydrate or solvate thereof, in combination with a corticoid.

Winquist discloses "A randomized, open-label multicentre study of XRP-6258 [cabazitaxel] at 25 mg/m^2 in combination with prednisone every 3 weeks . . . for the treatment of hormone-refractory metastatic prostate cancer previously treated with a Taxotere-containing regimen." Ex. 1009 at 3948. Winquist further discloses that the study is a "[r]andomized phase III" study coordinated by Sanofi-Aventis, targeting patients with "[h]ormone-refractory prostate cancer previously treated with docetaxel," and having a sample size of 720 patients, with "overall survival" as the primary endpoint of the study. *Id*. Thus, Winquist teaches a method for treating patients with mCRPC previously treated with docetaxel (Taxotere®), comprising administering cabazitaxel (XRP6258) in combination with the corticoid prednisone for the purpose of increasing overall survival. *See id*; *see also* Ex. 1002, ¶¶115-16. Winquist fully enabled this method, as the actions required to perform it were routine for a person of ordinary skill in the art. *Id.*

Winquist expressly discloses every element of claim 1, except that, instead of stating that the prostate cancer "has progressed during or after treatment with

docetaxel," Winquist discloses that the patient's "hormone-refractory metastatic prostate cancer" has been "previously treated with a Taxotere-containing regimen." As discussed by Dr. Seth, it was well known that a patient with hormone-refractory metastatic prostate cancer treated with a docetaxel regimen would almost certainly have developed resistance to the drug, leading to subsequent progression of the disease. *See* Ex. 1002, ¶¶ 65, 118. It is implicit in treatment of a patient with mCRPC who has previously been treated with docetaxel that further treatment is necessary ***because*** progression occurred during or after docetaxel treatment. Ex. 1002, ¶¶ 94, 117. Cabazitaxel was known to be a second-line treatment for use after docetaxel. Ex. 1002, ¶ 77. If docetaxel had stopped progression of the cancer, second-line treatment would be unnecessary. *See id.*, at ¶ 117. Thus, it would have been readily understood by a person of ordinary skill in the art at the relevant time that the treatment described by Winquist was a second-line treatment for patients whose cancer had "progressed during or after treatment with docetaxel."

The TROPIC Listing provides further description of the same Phase III clinical study described in Winquist, as evidenced by the similar title and identical sponsor, study design (administration with prednisone and compared to mitoxantrone), patient population, and stated objective. *Compare* Ex. 1008 with Ex. 1009; *see also* Ex. 1002, ¶¶ 118, 120-21. The TROPIC Listing provides further disclosure regarding patients whose cancer had progressed during or after treatment with docetaxel. Inclusion of patients in the TROPIC study required "[d]ocumented progression of disease" in the patients who were all, by design, previously treated with docetaxel. Ex. 1009 at 0002. The documented progression

included "a new lesion [or] rising PSA levels." *Id.* Because either a new lesion or a rising PSA level alone establishes progression, a patient previously treated with docetaxel who exhibits a *new* lesion or *rising* PSA levels must necessarily have prostate cancer that has progressed during or after docetaxel treatment. Ex. 1002, ¶ 119. Thus, the TROPIC Listing teaches treating patients with mCRPC that has progressed during or after treatment with docetaxel. *Id*. at 0001-02.

A person of ordinary skill in the art had good reasons to combine the teachings of Winquist and the TROPIC Listing because they were two disclosures of the same treatment method being used in the very same study. Moreover, a person of ordinary skill in the art would have had good reason to conclude that a 25 mg/m^2 dose of cabazitaxel administered in combination with prednisone would have anti-cancer activity when given to a patient with mCRPC that has progressed during or after docetaxel treatment, as disclosed in Winquist and the TROPIC Listing. As explained by Dr. Seth (Ex. 1002), it was known in the art that anti-cancer activity against docetaxel-resistant, castration-resistant prostate cancer was observed in patients treated with cabazitaxel. *See*, *e.g*., Ex. 1002, ¶¶ 66-69, discussing objective responses to cabazitaxel in Attard (Ex. 1021). Indeed, Attard described cabazitaxel (XRP6258) as showing improvement over paclitaxel and docetaxel with "higher therapeutic indices" and "activity against resistant tumours." Ex. 1021 at 74-75 & Table 3. The safety profile of cabazitaxel was also known to be "very favorable" compared to the marketed taxanes (*i.e.*, paclitaxel and docetaxel). Ex. 1010 at 1548, 1551.

As Dr. Seth testifies (Ex. 1002, ¶ 222), cabazitaxel's activity against prostate cancer was reasonably expected because of its many similarities with its close structural analogue, the known anti-prostate cancer drug docetaxel. For example, cabazitaxel is a taxane drug that was known in the art to target the same binding site (the "taxane-binding site") on beta-tubulin as other successful taxanes, such as docetaxel. *Id.*; *see also*, Attard *et al.*, Ex. 1021 at 75. Binding of taxanes (*e.g.*, docetaxel) at the taxane-binding site was understood to be effective both in breast cancer and in prostate cancer. *See* Ex. 1024 at 1, 35 ("Taxotere is a microtubule inhibitor used for: [metastatic] Breast Cancer . . . [and metastatic] Hormone Refractory Prostate Cancer."); *see also* Ex. 1021 at 72 (docetaxel leads to "superior survival" for prostate cancer patients and has "superior activity" against metastatic breast cancer); *id.* at 74 (taxanes "target the taxane-binding site"); Ex. 1002, ¶ 110 (docetaxel proved survival benefit of cytotoxic chemotherapy in CRPC patients).

Cabazitaxel was shown to have an acceptable 14% objective response rate among metastatic breast cancer patients in a Phase II clinical study, which results were known to have motivated a Phase III clinical study of cabazitaxel among metastatic prostate cancer patients Ex. 1002, ¶¶ 70-72; Ex. 1022 at 163. As of October 23, 2008, the TROPIC Listing discloses that the Phase III study of cabazitaxel among mCRPC patients had been continuing since December of 2006. Ex. 1008 at 0001-02; Ex. 1002, ¶ 122. One of ordinary skill would thus have had a well-founded reason to conclude that cabazitaxel was active against mCRPC that had progressed during or after treatment with docetaxel, as taught by Winquist and the TROPIC Listing. Ex. 1009 at 3948; Ex. 1008 at 0001-02; Ex. 1002, ¶¶ 120-21.

Absolute predictability is not required. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed.Cir.2007); *In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988).

As discussed above, *see supra* Section VI.G, the phrase "[a] method for treating" is not limiting because the patentee defined a structurally complete invention in the claim body and uses these phrases in the preamble only to state a purpose or intended use for the invention. *See Braintree Labs.*, 749 F.3d at 1357. However, even if the phrase were limiting, Winquist and the TROPIC Listing teach that the disclosed method is both a method of "treating" a patient and a method of "increasing survival of" a patient. For example, Winquist teaches administering cabazitaxel (XRP6258) in combination with prednisone "for the treatment of hormone-refractory metastatic prostate cancer previously treated with a taxotere-containing regimen." Ex. 1009 at 3948. The TROPIC Listing similarly teaches that the method is used "in the treatment of hormone refractory metastatic prostate cancer previously treated with Taxotere-containing regimen." Ex. 1008 at 0001. Winquist and the TROPIC Listing disclose that the primary objective is "overall survival." Ex. 1008 at 0001; Ex. 1009 at 3948; *see also* Ex. 1002, ¶ 132. Thus, even if the preamble phrase in claim 1 regarding the purpose of the method were limiting, Winquist and the TROPIC Listing render the purpose obvious.

2. Claim 2

Claim 2 depends from claim 1, and further recites "the prostate cancer is an advanced metastatic disease." Patent Owner has previously asserted in litigation that "advanced metastatic disease" includes "Castration resistant (hormone refractory), metastatic prostate cancer." Ex. 1031 at 00018. Winquist and the

TROPIC Listing each disclose "the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere-containing regimen" Ex. 1009 at 3948; Ex. 1008 at 0001. Under the Patent Owner's own construction, the "advanced metastatic disease" element is disclosed by the prior art method.

The TROPIC Listing provides additional disclosure that the treatment method was for an advanced metastatic disease. Patient inclusion criteria in the TROPIC study included "[d]ocumented progression of disease . . ." Ex. 1008 at 0002. In particular, progression included rising PSA levels following docetaxel treatment, *id.*, which indicates advanced disease. Ex. 1002, ¶¶ 49-50, 123; Ex. 1030 at S11. Further, the progression criteria included visceral lesions, which are indicators of advanced disease because the cancer has widely metastasized beyond the prostate and surrounding tissue. *Id.* Thus, treatment of advanced metastatic prostate cancer, as in claim 2, was obvious in view of the prior art.

3. Claims 7-9

Claims 7-9 depend from claim 1 and recite distributions of pharmacokinetic parameters resulting from administration of 25 mg/m^2 of cabazitaxel. Each of claims 7-9 recites that cabazitaxel is "administered in an amount to provide" a distribution of a pharmacokinetic parameter (AUC, C_{max}, or plasma clearance). The specification of the '592 patent states that these distributions of parameters were "[b]ased on pharmacokinetic analysis, after an intravenous dose of cabazitaxel **25 mg/m^2** every 3 weeks" Ex. 1001, col. 18, ll. 36-49 (emphasis added). Thus, claims 7-9 simply recite pharmacokinetic parameters that inherently follow as a direct result of administering cabazitaxel at 25 mg/m^2, addressed in

claim 1. Ex. 1002, ¶ 124. The '592 patent admits that these characteristics of cabazitaxel are inherent; for example, the '592 patent states that "cabazitaxel has a plasma clearance of 48.5 L/h . . . in patients with metastatic prostate cancer" Ex. 1001, col. 18, ll. 46-49; *see also id.* at col. 18, ll.36-41 (disclosing a C_{max} of 226 ng/mL and an AUC of 991 ng·h/mL for the same patient population); Ex. 1002, ¶ 124. Values within the claimed distributions necessarily would have resulted from performing the method disclosed by the TROPIC Listing and Winquist, using the dose of 25 mg/m^2 disclosed by Winquist. Ex. 1002, ¶¶ 56, 124. Thus, the distributions of pharmacokinetic parameters recited in claims 7-9 would have been obvious in view of the disclosure in Winquist of administering 25 mg/m2 of cabazitaxel to metastatic prostate cancer patients. Ex. 1002, ¶ 124.

4. Claim 13

Claim 13 depends from claim 1, and further recites, "wherein the corticoid is selected from the group consisting of prednisone and prednisolone." Winquist and the TROPIC Listing expressly teach administering cabazitaxel in combination with prednisone (Ex. 1009 at 3948; Ex. 1008 at 0001), and combining taxanes with prednisone for the treatment of prostate cancer was well known in the art. *See* Ex. 1002, ¶¶ 61-62. Thus, it would have been obvious to one of ordinary skill to treat prostate cancer by administering cabazitaxel in combination with prednisone, as taught by Winquist and the TROPIC Listing. Ex. 1002, ¶ 126.

5. Claims 17 and 20

Claims 17 and 20 depend from claim 1, and further require that the cancer be "a castration resistant or hormone-refractory prostate cancer." Claim 20 further

requires that the cancer be metastatic. Winquist and the TROPIC Listing each expressly teach a method for treating "hormone refractory metastatic prostate cancer" by administering cabazitaxel in combination with prednisone. Ex. 1009 at 3948; Ex. 1008 at 0001. Claims 17 and 20 are obvious in view of Winquist and the TROPIC Listing. Ex. 1009 at 3948; Ex. 1008 at 0001; Ex. 1002, ¶ 127.

6. Claim 24

Claim 24 depends from claim 1, and further recites, "wherein the prostate cancer is a castration resistant or hormone-refractory, metastatic prostate cancer, and wherein the corticoid is selected from the group consisting of prednisone and prednisolone, and wherein the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 25 mg/m^2." Each of these claim limitations have been discussed above in relation to claim 20 (mCRPC), claim 13 (prednisone), and claim 1 (25 mg/m^2), based on the disclosures of Winquist and the TROPIC Listing, and are obvious for the same reasons stated above.

7. Claim 27

Independent claim 27 differs from independent claim 1 in that (1) the preamble replaces the phrase "[a] method for treating a patient" with the phrase "[a] method of increasing survival of a patient," (2) the prostate cancer is mCRPC, and (3) specifies a prednisone or prednisolone corticoid. The limitations of the method of claim 1 are all present in claim 27, and their combination is obvious for the reasons stated above with respect to claim 1. For the reasons discussed above with respect to claims 2, 17, and 20, the limitation that the prostate cancer is mCRPC and the corticoid is prednisone does not render the claim patentable over

the method disclosed in Winquist and the TROPIC Listing. As discussed above for claim 1, Winquist fully enabled this method as the actions required to perform it were routine matters for a person of ordinary skill in the art. Ex. 1002, ¶ 132.

As discussed above, *see supra* Sections VI.H, the phrase "[a] method of increasing survival of" is not limiting. Even if limiting, as discussed above, *supra* section VIII.A.i.1, Winquist and the TROPIC Listing teach that the disclosed method is both a method of "treating" a patient and a method of "increasing survival of" a patient, and expressly disclose overall survival as the "primary objective" of administering cabazitaxel and prednisone to the patient population "for the treatment of" mCRPC previously treated with docetaxel. Ex. 1008 at 0001; Ex. 1009 at 3948; *see also* Ex. 1002, ¶ 132. Thus, even if the preamble phrase in claim 27 regarding the purpose of the method were deemed limiting, Winquist and the TROPIC Listing render the purpose obvious.

In addition to the express teachings of Winquist and the TROPIC Listing, there are other good reasons why one of ordinary skill in the art would have had a reasonable expectation that the treatment method of Winquist and the TROPIC Listing would increase overall survival. For example, it was known that docetaxel provided a survival benefit against mCRPC of 2.4 months. Ex. 1001 1:62-67 (background); *see also* Ex. 1021 at 72 (docetaxel leads to "superior survival" for prostate cancer patients); Ex. 1002, ¶ 110 (docetaxel proved survival benefit of cytotoxic chemotherapy in CRPC patients). As discussed above with respect to claim 1, it was known that cabazitaxel was a close analogue of docetaxel, shared its anti-cancer mechanism of action with docetaxel (which mechanism was

successful in treating both breast and prostate cancers), had an improved therapeutic index over docetaxel, and had demonstrated activity against docetaxel-resistant cancers, including a 14% objective response rate. *See supra* at Section VIII.A.i.1; Ex. 1002, ¶¶ 66-69, 120-21, 133, 169-70, 222; Ex. 1021 at 72, 74-75 & Table 3; Ex. 1022 at 163; Ex. 1024 at 1, 35; *see also* Ex. 1010 at 1548, 1551 (cabazitaxel's safety profile was "very favorable"). Thus, a person of ordinary skill in the art would reasonably expect cabazitaxel to exhibit a survival benefit against mCRPC. Ex. 1002 at 128-30. Absolute predictability is not necessary. *In re O'Farrell,* 853 F.2d at 903; *see also Pfizer,* 480 F.3d at 1364.

8. Claims 5, 19, 23, 25, and 29

Claims 5, 19, 23, 25, and 29 depend, respectively, from claims 1, 17, 20, 24, and 27 discussed above, and further recite that the claimed methods comprise "repeating the administration of [. . .] cabazitaxel, or hydrate or solvate thereof, as a new cycle every 3 weeks." The TROPIC Listing expressly discloses administering XRP6258 (cabazitaxel) "every three weeks for the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere-containing regimen." Ex. 1008 at 0001. Winquist also discloses administering "XRP-6258 at 25 mg/m^2 in combination with prednisone every three weeks." Ex. 1009 at 3948. The three week dose cycle implemented by Winquist and by the TROPIC Listing was not a new concept, being a standard practice for treatment of prostate cancer. *See* Ex. 1002, ¶¶ 60-61, discussing the Taxotere Label (Ex. 1024). Thus, in view of Winquist and the TROPIC Listing, one of ordinary skill in the art would have found it obvious and routine to administer cabazitaxel as a new cycle

every three weeks. Ex. 1002, ¶¶ 136-37.

9. Claims 12, 18, 22, and 28

Claims 12, 18, 22, and 28 depend, respectively, from claims 1, 17, 20, and 27 discussed above, and further recite that "the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 25 mg/m^2." Winquist expressly discloses administration of "XRP-6258 [cabazitaxel] at 25 mg/m^2." Ex. 1009 at 3948. Thus, as recited in claims 12, 18, 22, and 28, it would have been obvious to administer cabazitaxel at 25 mg/m^2, as disclosed by Winquist, in performing the treatment method disclosed therein and in the TROPIC Listing. Ex. 1002, ¶¶ 138-39.

In view of the foregoing, each of claims 1, 2, 5, 7-9, 12, 13, and 17-20, 22-25, and 27-29 of the '592 patent is made obvious under 35 U.S.C. § 103 by the combined teachings of Winquist and the TROPIC Listing. The claim chart below identifies where the specific elements of the claims are found in the references, and provides supporting citations to the declaration of Dr. Seth.

Challenged Claims	**Obvious over Winquist and the TROPIC Listing**
1. A method for treating a patient with prostate cancer	Ex. 1009 (open clinical trials) at 3948 ("[T]reatment of hormone-refractory metastatic prostate cancer"); *id.* (Patient population); *see also* Ex. 1008 at 0001; Ex. 1002 ¶¶ 115-19.
that has progressed during or after treatment with docetaxel	"Documented progression of disease" Ex. 1008 at 0002; Ex. 1002 ¶ 117. "[P]reviously treated with a Taxotere-containing regimen." *Id.* at 0001; Ex. 1009 at 3948. Ex. 1002 ¶ 119.
comprising administering to said patient	"Drug: XRP6258." Ex. 1008 at 0002.

a dose of 20 to 25 mg/m^2 of cabazitaxel . . .	"XRP-6258 at 25 mg/m^2." Ex. 1009 at 3948; Ex. 1002, ¶¶ 115, 119.
in combination with a corticoid.	XRP6258 in combination with prednisone." Ex. 1008 at 0001; Ex. 1009 at 3948; *see also* Ex. 1002, ¶116.
2. The method according to claim 1, where the prostate cancer is an advanced metastatic disease.	Hormone refractory metastatic prostate cancer previously treated with docetaxel. Ex. 1009 at 3948; Ex. 1008 at 0001. Ex. 1008 at 0002 (visceral lesions, new lesions, and rising PSA levels). *See also* Ex. 1002, ¶123.
5. The method according to claim 1, comprising repeating the administration of cabazitaxel . . . as a new cycle every 3 weeks.	"XRP6258 in Combination With Prednisone Every 3 Weeks." Ex. 1009 at 3948; Ex. 1008 at 0001; Ex 1002, ¶ 137.
7. The method according to claim 1, wherein said cabazitaxel . . . is administered in an amount to provide an AUC of about 991 ng·h/mL (CV 34%).	"XRP-6258 at 25 mg/m^2," Ex. 1009 at 3948; Ex 1002, ¶¶ 124-25.
8. The method according to claim 1, wherein said cabazitaxel . . . is administered in an amount to provide an C_{max} of about 226 ng·h/mL (CV 107%).	"XRP-6258 at 25 mg/m^2," Ex. 1009 at 3948; Ex 1002, ¶¶ 124-25.
9. The method according to claim 1 wherein said cabazitaxel . . . is administered in an amount to provide a plasma clearance of 48.5 L/h (CV 39%).	"XRP-6258 at 25 mg/m^2," Ex. 1009 at 3948; Ex 1002, ¶¶ 124-25.
12. The method according to claim 1, where the cabazitaxel . . . is administered at a dose of 25 mg/m^2	"XRP-6258 at 25 mg/m^2," Ex. 1009 at 3948; Ex 1002, ¶ 139.
13. The method according to claim 1, wherein the corticoid is selected from the group consisting of prednisone and	XRP6258 in Combination With Prednisone. Ex. 1008 at 0001; Ex. 1009 at 3948; *see also* Ex. 1002, ¶126.

prednisolone.	
17. The method according to claim 1, where the prostate cancer is a castration resistant or hormone-refractory prostate cancer.	"[H]ormone refractory metastatic prostate cancer" Ex. 1009 at 3948; Ex. 1008 at 0001; Ex 1002, ¶ 128.
18. The method according to claim 17, where the cabazitaxel . . . is administered at a dose of 25 mg/m^2.	"XRP-6258 at 25 mg/m^2" Ex. 1009 at 3948; Ex 1002, ¶ 139.
19. The method according to claim 17, comprising repeating the administration of said cabazitaxel . . . as a new cycle every 3 weeks.	"XRP-6258 . . . Every 3 Weeks." Ex. 1009 at 3948; Ex. 1008 at 0001;Ex 1002, ¶ 137.
20. The method according to claim 1, wherein the prostate cancer is a castration resistant or hormone-refractory, metastatic prostate cancer.	"[H]ormone refractory metastatic prostate cancer" Ex. 1009 at 3948; Ex. 1008 at 0001; Ex 1002, ¶ 127.
22. The method according to claim 20, where cabazitaxel . . . is administered at a dose of 25 mg/m^2.	"XRP-6258 at 25 mg/m^2" Ex. 1009 at 3948; Ex 1002, ¶ 139.
23. The method according to claim 20, comprising repeating the administration of said cabazitaxel . . . as a new cycle every 3 weeks.	"XRP-6258 . . . Every 3 Weeks." Ex. 1009 at 3948; Ex. 1008 at 0001; Ex 1002, ¶ 137.
24. The method according to claim 1, wherein the prostate cancer is a castration resistant or hormone-refractory, metastatic prostate cancer, and wherein the corticoid is selected from the group consisting of prednisone and prednisolone, and wherein the cabazitaxel . . . is administered at a dose of 25 mg/m^2.	Ex. 1008 at 0001 ("XRP-6258 at 25 mg/m^2 in combination with prednisone . . . for the treatment of hormone-refractory metastatic prostate cancer."); Ex. 1009 at 3948. *See also* Ex 1002, ¶¶ 128-30.
25. The method according to claim 24, comprising repeating the administration of said cabazitaxel . . . as a new cycle	"XRP-6258 . . . Every 3 Weeks." Ex. 1009 at 3948; Ex. 1008 at 0001; Ex 1002,

every 3 weeks.	¶ 137.
27. A method of increasing the survival of a patient with a castration resistant or hormone refractory, metastatic prostate cancer	*See* first box above for claim 1. "The primary objective is overall survival." Ex. 1008 at 0001; Ex. 1009 at 3948 (primary endpoint). *See also* Ex. 1002, ¶¶ 132-33.
that has progressed during or after treatment with docetaxel,	*See* second box above for claim 1; *see also* Ex. 1002, ¶¶ 131, 117, 119.
comprising administering a dose of 20 to 25 mg/m^2 of cabazitaxel . . . to the patient	*See* third box above for claim 1; *see also* Ex. 1002, ¶¶ 131, 115.
in combination with prednisone or prednisolone.	*See* fourth box above for claim 1; *see also* Ex. 1002, ¶ 135.
28. The method according to claim 27, where the cabazitaxel . . . is administered at a dose of 25 mg/m^2.	"XRP-6258 at 25 mg/m^2" Ex. 1009 at 3948; Ex 1002, ¶ 139.
29. The method according to claim 27, comprising repeating the administration of said cabazitaxel . . . as a new cycle every 3 weeks.	"XRP-6258 . . . Every 3 Weeks." Ex. 1009 at 3948; Ex. 1008 at 0001; Ex 1002, ¶ 137.

ii. [Ground 2] Claims 3-4: Obvious over Winquist, the TROPIC Listing, and Didier.

Ground 2 addresses the obviousness of claims 3 and 4. Claim 3 depends from claim 1, and further recites, "the cabazitaxel is in the form of an acetone solvate." Claim 4 depends from claim 3 and further recites, "the acetone solvate contains between 5% and 8% by weight of acetone."

Neither the TROPIC Listing nor Winquist teaches cabazitaxel in the form of an acetone solvate. Didier, however, teaches an acetone solvate of cabazitaxel, and discloses a "mean value of the content of acetone is 7%, which represents approximately the acetone stoichiometry, which is 6.5%, for a solvate comprising

one molecule of acetone." Ex. 1011 at col. 2, ll. 39-42; abstract. Claim 2 of Didier is to an acetone solvate of cabazitaxel "comprising from about 5 to about 7 percent by weight of acetone." *Id.* at col. 4, ll. 1-5. Thus, Didier teaches cabazitaxel in the form of an acetone solvate, containing, *e.g.*, from about 5% to about 7% by weight of acetone. *Id.* Didier also states that cabazitaxel "exhibits noteworthy anticancer and antileukemic properties," thus recognizing the therapeutic significance of the compound. *Id.* at col. 1, ll. 22-23; Ex. 1002, ¶ 141.

It was well known in the art that non-aqueous solvates such as acetone can be used to improve the water solubility of otherwise water-insoluble drugs, thereby enabling them to be dissolved in aqueous solutions suitable for intravenous administration. *See* Ex. 1002, ¶¶ 80-81, discussing Liu (Ex. 1025). It was also well known that taxanes are highly lipophilic and water-insoluble drugs. *Id.* As taught by the TROPIC Listing, cabazitaxel is administered via intravenous (IV) infusion. Ex. 1008 at 0002. Thus, one of ordinary skill in the art would have had strong reasons to prepare cabazitaxel in the form of a solvate, so as to enable the drug's dissolution into an aqueous solution suitable for intravenous infusion into a patient. Ex. 1002, ¶ 142. In view of Didier, the person of ordinary skill would have been motivated to select acetone as the choice of solvate, and in particular to use a solvate containing 7% by weight of acetone with a reasonable expectation of success, because such a solvate of cabazitaxel had been expressly described and validated by Didier. Ex. 1011 at col. 2, ll. 39-42; col. 4, ll. 1-5; Ex. 1002, ¶ 142. Thus, the cabazitaxel being "in the form of an acetone solvate" as recited in claim 3, and containing "between 5% and 8% by weight of acetone" as recited in claim 4,

would have been obvious to one of ordinary skill in the art in view of the combined teachings of Winquist, the TROPIC Listing, and Didier. *Id.*

iii. [Ground 3] Claims 7-9: Obvious over Winquist, the TROPIC Listing, and Mita.

Ground 3 addresses the obviousness of claims 7-9. Each of claims 7-9 recites that cabazitaxel is "administered in an amount to provide" a distribution of a pharmacokinetic parameter (respectively, "AUC of about 991 ng·h/mL (CV 34%)," "C_{max} of about 226 ng·h/mL (CV 107%)," and "plasma clearance of 48.5 L/h (CV 39%)"). As discussed in Ground 1, claims 7-9 recite distributions of pharmacokinetic parameters that are merely a result of administering cabazitaxel at a dose of 25 mg/m^2 every three weeks. *See* Ex. 1002, ¶ 56, discussing Ex. 1001, col. 18, ll. 36-49. This dosage is disclosed by Winquist, and necessarily results in pharmacokinetic parameters within the distribution ranges recited in claims 7-9. Ex. 1009 at 3948; Ex. 1002, ¶ 124.

In addition, Mita describes results of a pharmacokinetic study of cabazitaxel, and expressly teaches values of AUC, C_{max}, and plasma clearance that are within the claimed distribution ranges. Ex. 1012 at 729; Ex. 1002, ¶¶ 146-47. The pharmacokinetic parameters disclosed by Mita were obtained by administering cabazitaxel at doses of 20 mg/m^2 and 25 mg/m^2, doses falling within the range recited in claim 1, from which claims 7-9 depend. Ex. 1012 at 729; Ex. 1002, ¶¶ 145-47. For doses of 20 mg/m^2 and 25 mg/m^2 of cabazitaxel, Mita discloses AUC values of 766 ng•h/mL and 1,038 ng•h/mL, respectively. Ex. 1012 at 729. These values fall within the claimed range of about 991 ng•h/mL (CV34%) recited in

claim 7 (*i.e.*, 766 and 1,038 fall within 991±337). Ex. 1002, ¶¶ 145-47. For the dose of 20 mg/m^2, Mita discloses a C_{max} of 222 ng/mL. Ex. 1012 at 729. This value falls within the claimed range of about 226 ng/mL(CV107%) recited in claim 8 (*i.e.*, 222 ng/mL falls within 226 ±242 ng/mL). Ex. 1002, ¶¶ 146-48. Mita also discloses plasma clearance values of 58.2 L/h and 49.0 L/h for doses of 20 mg/m^2 and 25 mg/m^2, respectively. *See id.*, discussing Ex. 1012 at 729. These values fall within the claimed range of about 48.5 L/h (CV 39%) recited in claim 9 (*i.e.*, 58.2 L/h and 49.0 L/h fall within 48.5±18.9 L/h). *Id.* Because Mita disclosed values of AUC, C_{max} and plasma clearance resulting from administration of cabazitaxel to patients within the claimed ranges, the distribution ranges recited in claims 7-9 of the '592 patent are minor and obvious limitations in view of the prior art. Ex. 1002, ¶¶ 145-48.

iv. [Ground 4] Claims 10-11, 14, and 16: Obvious over Winquist, the TROPIC Listing, and Tannock.

Ground 4 addresses the obviousness of claims 10, 11, 14, and 16. Claims 10 and 11 depend from claim 1 and are directed to monitoring neutrophil levels while administering cabazitaxel. Claims 14 and 16 depend from claim 13 and recite doses of prednisone at 10 mg/day and cabazitaxel at 25 mg/m^2.

1. Claims 10 and 11

Claim 10 depends from claim 1 and further comprises "monitoring blood counts and measuring neutrophil levels in the patient." Claim 11 depends from claim 10 and further recites "discontinuing cabazitaxel treatment in a patient with a neutrophil count of ≤1,500 cells/mm^3." Tannock discloses successful Phase III

clinical studies of docetaxel for treating mCRPC, a taxane drug active against the same anti-cancer taxane binding site as cabazitaxel, in combination with prednisone. Ex. 1013 at 1502; Ex. 1002, ¶ 150. Tannock teaches monitoring neutrophil counts when administering a taxane drug to mCRPC patients, and discontinuing treatment if the count is less than 1,500 cells/mm^3. *Id.*; Ex. 1002, ¶ 150.

Monitoring neutrophil counts in patients receiving taxane therapy and discontinuing taxane treatment if counts fell below 1,500 cells/mm^3 was a minor and obvious limitation in view of the prior art. Neutrophils are a type of white blood cell. Ex. 1002, ¶ 61. Because the immune system needs to rapidly replenish neutrophils, they are particularly vulnerable to taxane activity preventing cell mitosis. *Id.* In the context of administering taxane drugs as chemotherapy in the treatment of cancer, the need to monitor blood counts and measure neutrophil levels and discontinue treatment when neutrophil levels fell too low was well known in the art. *See id.* According to Tannock, "[a] dose reduction or treatment delay was . . . stipulated for patients who had an **absolute neutrophil count of less than 1500 per cubic millimeter**." Ex. 1013 at 1504 (emphasis added). One of ordinary skill would have been motivated to monitor neutrophil counts, as disclosed by Tannock, in order to minimize the occurrence of adverse events in the patients being treated. Ex. 1013 at 1504; Ex. 1002, ¶ 151.

2. Claims 14 and 16

Claim 14 depends from claim 13, discussed above in Ground 1, and further recites "the prednisone or prednisolone is administered at a dose of 10 mg/day." As discussed in Ground 1, Winquist and the TROPIC Listing both teach

administering cabazitaxel in combination with prednisone. Ex. 1008 at 0001; Ex. 1009 at 3948. The Phase III study by Tannock, directed to treating metastatic prostate cancer with docetaxel and prednisone, teaches administering prednisone at a dose of 10 mg/day. Ex. 1013 at 1502, 1504. According to Tannock, and consistent with what was known in the art, this dose of prednisone provides palliative care to some patients with prostate cancer. *Id*. at 1503; Ex. 1002, ¶ 153. One of ordinary skill would have had a strong rationale to continue using the same dose of 10 mg/day prednisone described by Tannock to maintain palliative relief to patients . Ex. 1002, ¶ 152-53; Ex. 1008 at 0001; Ex. 1013 at 1502, 1504. The person of ordinary skill would have done so with a reasonable expectation of success since this dose of prednisone had already been well established for palliative treatment of patients undergoing taxane treatment for prostate cancer. Ex. 1013 at 1502, 1504; Ex. 1002, ¶ 153.

Claim 16 depends from claim 14 and further recites administering cabazitaxel at a dose of 25 mg/m^2. As discussed in Ground 1, this dose of cabazitaxel was disclosed by Winquist, and would have been obvious to use in performing the method of treatment disclosed by Winquist and the TROPIC Listing. Ex. 1009 at 3948, 1550; Ex. 1008 at 0001; Ex. 1002, ¶ 154.

Claims 14 and 16 would have been obvious to one of ordinary skill in view of the combined teachings of the TROPIC Listing, Winquist, and Tannock.

v. [Ground 5] Claims 21, 26, and 30: Obvious over Winquist, the TROPIC Listing, and Pivot.

Ground 5 addresses the obviousness of claims 21, 26, and 30, which depend

from claims 20, 1, and 27 respectively and recite a 20 mg/m^2 dose of cabazitaxel. Pivot discloses administering cabazitaxel "at 20 mg/m^2, given as a 1-h i.v. infusion on day 1 every 3 weeks." Ex. 1010 at 1548. Pivot explains that the 20 mg/m^2 dose was the "recommended dose for phase II and III studies" from the Phase I studies. *Id*; *see* Ex. 1002, ¶ 157. Pivot further discloses that, in the Phase II study, cabazitaxel was initially administered at a 20 mg/m^2 dose, and thereafter "escalat[ed] up to 25 mg/m^2 from cycle 2, in selected patients, on the basis of their good tolerance in cycle 1" for 28% of patients treated without increasing adverse events. Ex. 1010 at 1550. Based on the study data, in which 72% of patients were only treated at 20 mg/m^2, Pivot determined that cabazitaxel "was active and well tolerated in . . . patients with taxane-resistant disease." *Id*. at 1547.

In light of Pivot's teaching that some patients would not tolerate the higher dose of 25 mg/m^2, it would have been readily appreciated by one of ordinary skill in the art to administer the lower dose of 20 mg/m^2 at first before administering the higher dose of 25 mg/m^2. Ex. 1002, ¶ 158. Thus, a person of ordinary skill in the art would have found it obvious to administer cabazitaxel at a dose of 20 mg/m^2, as disclosed by Pivot, in performing the method of treating prostate cancer disclosed by Winquist and the TROPIC Listing. *Id.*

vi. [Ground 6] Claim 15 : Obvious over Winquist, the TROPIC Listing, Pivot, and Tannock.

Ground 6 addresses the obviousness of claim 15. Claim 15 depends from claim 14 and recites a 20 mg/m^2 dose of cabazitaxel. The dose of 20 mg/m^2 of cabazitaxel is addressed above in the context of claims 21, 26 and 30 in Ground 5.

The 10 mg/day dose of prednisone is addressed above in the context of claim 14 in Ground 4. The same analyses apply here. It would have been obvious to treat prostate cancer as taught by Winquist and the TROPIC Listing using the dose of 20 mg/m^2 of cabazitaxel taught by Pivot (at, *e.g.*, Ex. 1010 at 1547) in combination with the dose of 10 mg/day of prednisone taught by Tannock (at, *e.g.*, Ex. 1013 at 1504), as recited in claim 15. Ex. 1002, ¶ 160.

B. Grounds Asserting Winquist and Pivot.

i. [Ground 7] Claims 1-2, 5, 7-9, 12-13, and 17-30: Obvious over Winquist and Pivot.

Winquist teaches administering cabazitaxel "at 25 mg/m^2 in combination with prednisone every 3 weeks . . . for the treatment of hormone-refractory metastatic prostate cancer previously treated with [docetaxel]" with a primary endpoint of "overall survival." *Id.* Winquist thus teaches administration of "20 to 25 mg/m^2 of cabazitaxel," as in claims 1 and 27, as well as the 25 mg/m^2 dose of claims 12, 18, 22, 24, and 28, for treating and increasing survival of a patient with mCRPC previously treated with docetaxel. Ex. 1002, ¶¶ 162-64, 193-96.

Pivot discloses the treatment of docetaxel-resistant metastatic breast cancer by administering cabazitaxel "every 3 weeks at 20 mg/m^2 (then, in the absence of severe toxicity, at 25 mg/m^2)." Ex. 1010 at 1547. Pivot also teaches administering the 20-25 mg/m^2 cabazitaxel doses to patients having cancer that has progressed during or after treatment with docetaxel. For example, Pivot teaches: "Resistance to previous taxane-containing chemotherapy was required [for inclusion in the study]. This resistance was defined as: for advanced disease; progressive disease

(PD) as the best overall response after first- or second-line treatment." Ex. 1010 at 1548. Nearly two-thirds (65%) of the patients had been last treated with docetaxel. Ex. 1010 at 1549 (Table 1); Ex. 1002 ¶ 165. Thus, Pivot teaches administering cabazitaxel to patients whose cancer was classified as resistant because progression was observed after docetaxel treatment. Ex. 1002 ¶ 167.

One of ordinary skill in the art would have had reason to perform the method of treatment described by Winquist using the lower dose of 20 mg/m^2 of cabazitaxel (recited in claims 21, 26, and 30) for patients with lower tolerance for the drug, as described by Pivot, in order to minimize adverse events yet achieve efficacy. Ex. 1002, ¶¶ 169, 190-92. The person of ordinary skill would have had a reasonable expectation of success in administering cabazitaxel at both doses (20 mg/m^2 and at 25 mg/m^2) for prostate cancer because both doses had been used by Pivot and established as falling within a safe and therapeutically effective range. Ex. 1009 at 3948; Ex. 1010 at 1547-48, 1550; Ex. 1002, ¶¶ 168-169.

A person of ordinary skill in the art would have viewed the results of the breast cancer study disclosed in Pivot as probative of activity against mCRPC because cabazitaxel was known to share the same mechanism of action as docetaxel, which was successful in treating both metastatic breast cancer and metastatic hormone refractory prostate cancer and increasing patient survival. *See*, *e.g.*, Ex. 1021 at 72, 74-75; Ex. 1024 at 1, 35; Ex. 1002, ¶¶ 222, 110. Further, a skilled artisan would reasonably expect cabazitaxel to be active against docetaxel-resistant cancer because this property of cabazitaxel was known and cabazitaxel was selected for development ***because*** of this property. Ex. 1010 at 1547; Ex. 1002

¶¶ 171-72, *see also* ¶¶ 66-69 (discussing Ex. 1021). In light of the background knowledge that cabazitaxel was active against docetaxel-resistant tumors and shared the same mechanism of action as docetaxel (which was known to be active against both metastatic breast cancer and mCRPC), and Pivot's disclosure that 20 mg/m^2 of cabazitaxel was effective against docetaxel-resistant metastatic breast cancer, it was not surprising or unexpected that cabazitaxel was also active against docetaxel-resistant mCRPC. Ex. 1002, ¶¶ 73, 220-221. Absolute predictability is not necessary. *In re O'Farrell,* 853 F.2d at 903; *see also Pfizer,* 480 F.3d at 1364.

Moreover, it was known in the art well before October 29, 2009 that the prostate cancer study disclosed in Winquist was based on the success of the breast cancer study disclosed in Pivot. Ex. 1002, ¶¶ 70-72, discussing Beardsley, Ex. 1022. Beardsley noted that the 14% response rate from the Pivot study was adequate to justify Phase III studies ***among prostate cancer patients***. Ex. 1022 at 163; Ex. 1010 at 1551 (14%). Pivot also confirmed that the safety profile of cabazitaxel at 20 and 25 mg/m^2 doses was "very favorable" compared to the marketed taxanes (*i.e.*, paclitaxel and docetaxel). Ex. 1010 at 1548, 1551.

As discussed in greater detail above, Winquist, in view of Pivot, fully enabled the method disclosed therein, as the actions required to perform the method were routine matters for a person of ordinary skill in the art. Ex. 1002, ¶¶169, 183.

With respect to claims 7, 8, and 9, as discussed above in Ground 1, these pharmacokinetic distributions result inherently from administration of cabazitaxel to human patients at 25 mg/m^2, a dose that is expressly disclosed by both Winquist

and Pivot. *See supra* Section II; Ex. 1001, col. 18, ll. 36-49; Ex. 1002, ¶¶ 174-75. With respect to claims to the prostate cancer being "advanced," "metastatic," and "castration resistant or hormone-refractory" (one or more of which are recited, *e.g.*, in claims 2, 17, 20, 24, and 27), this indication would also have been obvious to one of ordinary skill in view of Winquist's explicit teaching to treat "hormone-refractory metastatic prostate cancer previously treated with [docetaxel]" with cabazitaxel, and Pivot's disclosure of treating cancer that was both "metastatic" and "advanced" by administering cabazitaxel. Ex. 1002, ¶¶ 173, 177-81; Ex. 1009 at 3948; Ex. 1010 at 1547-49. Winquist and Pivot also both expressly disclose administering cabazitaxel "every three weeks" (recited in claims 5, 19, 23, 25, and 29), and Winquist further teaches that the cabazitaxel is administered "in combination with prednisone" (recited in claims 13, 24, and 27). Ex. 1009 at 3948; Ex. 1010 at 1547; Ex. 1002, ¶¶176-89.

In view of the foregoing, each of claims 1, 2, 5, 7-9, 12, 13, and 17-30 of the '592 patent is obvious under 35 U.S.C. § 103 by the combined teachings of Winquist and Pivot. The claim chart below identifies where the specific elements of independent claims 1 and 27 are found in the references, and provides supporting citations to the declaration of Dr. Seth.

Challenged Claims	Obvious over Winquist and Pivot
1. A method for treating a patient with prostate cancer	Ex. 1009 (open clinical trials) at 3948 ("[T]reatment of hormone-refractory metastatic prostate cancer"); *id.* (Patient population). Ex. 1002 ¶¶ 162-64.
that has progressed during or after treatment with docetaxel	Prior docetaxel treatment. Ex. 1009 at 3948; Ex. 1010 at 1549 & Table 1 (65%). Active in docetaxel-resistant cancer. Ex. 1010 at

	1551. "Progressive disease . . . after first- or second-line treatment." Ex. 1010 at 1548. *See also* Ex. 1002, ¶¶162, 165-67.
comprising administering to said patient a dose of 20 to 25 mg/m^2 of cabazitaxel	Ex. 1009 at 3948 (25 mg/m^2); Ex. 1010 at 1547 (20 mg/m^2), 1150 ("Dose escalation up to 25 mg/m^2"). *See also* Ex. 1002, ¶¶ 162, 168-69.
. . . in combination with a corticoid.	"XRP-6258 at 25 mg/m^2 in combination with prednisone . . . ." Ex. 1009 at 3948; Ex. 1002, ¶ 163.
27. A method of increasing the survival of a patient with a castration resistant or hormone refractory, metastatic prostate cancer	*See* first box above for claim 1 in Ground 7. Ex. 1009 at 3948 ("[P]rimary endpoint: . . . overall survival"); *see also* Ex. 1010 at 1549 (overall survival endpoint), 1547 (12.3 months). *See also* Ex 1002, ¶¶ 183-84.
that has progressed during or after treatment with docetaxel,	*See* second box above for claim 1 in Ground 7; *see also* Ex. 1002, ¶ 185.
comprising administering a dose of 20 to 25 mg/m^2 of cabazitaxel . . . to the patient	*See* third box above for claim 1 in Ground 7; *see also* Ex. 1002, ¶¶ 182, 162, 168-69.
in combination with prednisone or prednisolone.	*See* fourth box above for claim 1 in Ground 7; *see also* Ex. 1002, ¶ 186.

ii. [Ground 8] Claims 3-4: Obvious over Winquist, Pivot, and Didier.

Ground 8 differs from Ground 2 in relying on Pivot rather than the TROPIC Listing. As discussed in more detail in Ground 2, Didier teaches cabazitaxel in the form of an acetone solvate, as recited in dependent claim 3, and teaches the acetone solvate containing percentages by weight of acetone falling within the range recited in dependent claim 4. Ex. 1011 at col. 2, ll. 39-42; *see also id*. at abstract and claim 2. As discussed in Ground 2, one of ordinary skill would have had a strong reason to administer cabazitaxel according to the method disclosed in Winquist, using a solvate to improve cabazitaxel's solubility in water as disclosed

in Didier, thereby making it suitable for IV infusion. Ex. 1002, ¶ 198; Ex. 1010 at 1548.

iii. [Ground 9] Claims 7-9: Obvious over Winquist, Pivot, and Mita.

Ground 9 differs from Grounds 1 and 3 in relying on Pivot rather than the TROPIC Listing, and from Ground 1 in relying on Mita to establish disclosure of pharmacokinetic values within the claimed distributions. As discussed in more detail in Ground 3, Mita discloses pharmacokinetic parameters resulting from administration of cabazitaxel at doses of 20 mg/m^2 and 25 mg/m^2, and reports values of AUC, C_{max}, and plasma clearance that fall within the distributions recited in dependent claims 7, 8, and 9, respectively. Ex. 1012 at 729; Ex. 1002, ¶¶ 200-02. In view of Winquist and Pivot, it would have been obvious to treat mCRPC with cabazitaxel using doses of 20 and 25 mg/m^2. Because the disclosed values fall within the distributions recited in claims 7-9, the claimed distributions would have been obvious to one of ordinary skill. *Id.*

iv. [Ground 10] Claims 10-11 and 14-16: Obvious over Winquist, Pivot, and Tannock.

1. Claims 10 and 11

Ground 10 differs from Grounds 4 and 6 in relying on Pivot rather than the TROPIC Listing. As discussed in greater detail in Ground 4, Tannock discloses administering docetaxel to patients with mCRPC, and discloses monitoring blood counts and measuring neutrophil levels, as recited in dependent claim 10, and discontinuing treatment if the neutrophil count is less than 1,500 cells per cubic millimeter, as recited in dependent claim 11. Ex. 1013 at 1504; Ex. 1002, ¶ 206. In

the context of administering taxane drugs, as discussed above in Grounds 4 and 6, it would have been obvious to monitor blood counts and measure neutrophil levels as disclosed by Tannock, and to use the well-established neutrophil concentration of 1,500 cells/mm^3, also disclosed by Tannock, as the threshold for discontinuing treatment in order to minimize adverse events. Ex. 1002, ¶¶ 207-08.

2. Claims 14-16

As discussed in greater detail in Ground 4, Winquist teaches administering prednisone with cabazitaxel and Tannock teaches administering prednisone at a dose of 10 mg/day, as recited in claim 14, in combination with docetaxel, for the treatment of mCRPC. Ex. 1013 at 1502, 1504. Tannock teaches that this dose of prednisone is used to provide palliative care to patients with prostate cancer. *Id*. at 1503. One of ordinary skill would thus have had a strong rationale to continue using 10 mg/day prednisone as described by Tannock to maintain palliative relief when treating prostate cancer with cabazitaxel as taught by Winquist. Ex. 1002, ¶ 209-10; Ex. 1013 at 1502, 1504; Ex. 1009 at 3948.

As discussed in greater detail in Ground 7, the doses of 20 and 25 mg/m^2 of cabazitaxel recited in claims 15 and 16, respectively, were determined by Pivot to be safe and effective, and the skilled artisan would have desired to use the same doses in the treatment disclosed by Winquist, which also discloses the dose of 25 mg/m^2. Ex. 1010 at 1548, 1550; Ex. 1009 at 3948; Ex. 1002, ¶ 211-12. Accordingly, claims 14-16 would have been obvious to one of ordinary skill in view of the combined teachings of Winquist, Pivot, and Tannock.

IX. PHASE III CLINICAL DATA ARE NOT REQUIRED TO HAVE A REASONABLE EXPECTATION OF SUCCESS IN AN OBVIOUSNESS ANALYSIS

During prosecution, Patent Owner argued that a person of ordinary skill in the art would not have had a reasonable expectation that the Phase III study of cabazitaxel for treating prostate cancer referred to in Beardsley would succeed in returning statistically significant results over the reference treatment. *See, e.g.*, Ex. 1004 at 00146-48, 00181, 00185, 00187, 00190. However, clinical data obtained from a known method of administering a known compound to treat a known indication is not patentable because "efficacy is inherent in carrying out the claim steps." *See In re Montgomery*, 677 F.3d 1375, 1381 (Fed. Cir. 2013). The '592 patent confirms that the Phase III efficacy and safety data disclosed therein are inherent, measurable properties of cabazitaxel. *See* Ex. 1001, col. 9, ll. 32-35 ("the efficacy and safety of cabazitaxel in combination with prednisone were evaluated . . . ."); *see also* Ex. 1002 at 44. The Federal Circuit has "repeatedly held that 'newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.'" *Id.* (quoting *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001)). This is true even if the prior art "merely proposed" the method at an advanced state of testing designed to secure regulatory approval (without actually doing so). *See id.* at 1382. This is why "[i]t is well established that a patent may be secured, and typically is secured, before the conclusion of clinical trials." *Id.* Indeed, the Federal Circuit has noted that proper Patent Office procedure presumes that even the ***initiation*** of human clinical trials for a therapeutic product or process is

"reasonably predictive of having the asserted therapeutic utility." *Id.* at 1382-83 (quoting M.P.E.P. § 2107.03 (8th ed., rev. 6, Sept. 2007)).

In addition, whether or not the clinical study would ultimately yield statistically significant Phase III human clinical results does not bear on patentability. Instead, the relevant question is whether one of ordinary skill in the art would have a reasonable expectation of success in practicing the claimed method based on the teachings of the asserted references and the general background knowledge in the art. As discussed above, *e.g.*, sections VIII.A.i.1, 7 and VIII.B.i, a skilled artisan would have a reasonable expectation of success in practicing the claimed method based on the teachings of the asserted references and the general background knowledge in the art.

Finally, the Patent Owner's argument during prosecution that there can be no reasonable expectation of success for a Phase III clinical study is contradicted by Patent Owner's own cited reference. The applicant relied on the Sartor declaration (Ex. 1004 at 00164-92), which cites a 2003 article from Booth, and asserts that "[w]hen studies more often fail than succeed, calling positive results reasonably expected is simply scientifically wrong." Ex. 1004 at 00168. But according to Booth *et al.*—the very source relied upon by Dr. Sartor—more than 60% of oncology drugs that are successful at Phase II are also successful at Phase III. Ex. 1015 at 610 & (Figure 1). Phase III clinical studies are conducted ***because*** they have a reasonable expectation of success in view of positive results from Phase II, Phase I, and preclinical studies that indicate that the treatment will be safe and effective. Ex. 1002 ¶ 224. As Dr. Seth explains, the unpredictability of clinical

results was most acute in Phases I and II, particularly for novel targets, not for Phase III studies of drugs directed to well-known targets. Ex. 1002 ¶¶ 221-22.

Further, a skilled artisan had good reason to expect that the TROPIC study in particular would succeed. For example, cabazitaxel was known to share the same mechanism of action as docetaxel, which was successful in treating both breast and prostate cancers. *See*, *e.g.*, Ex. 1021 at 72, 74-75; Ex. 1024 at 1, 35; Ex. 1002, ¶ 222. Indeed, the art recognized that the Phase III study described in Winquist and the TROPIC Listing, which references were not considered by the examiner, was being conducted in view of the drug's activity against other docetaxel-refractory cancers. *See* Ex. 1002, ¶¶ 70-72, discussing Beardsley (Ex. 1022). As Beardsley discloses, cabazitaxel was shown to have a 14% objective response rate. Ex. 1022 at 168. It was known in the art that a 14% response rate indicated a high likelihood of Phase III success. S*ee* Ex. 1002, ¶¶ 71, 98, discussing Ex. 1023 (El-Maraghi). The Phase II study also evaluated the safety profile of cabazitaxel at 20 and 25 mg/m^2 doses and concluded that it was "very favorable" compared to the marketed taxanes (*i.e.*, paclitaxel and docetaxel). Ex. 1010 at 1548, 1551. Indeed, Attard described cabazitaxel (XRP6258) as one of the compounds having "higher therapeutic indices" than docetaxel. Ex. 1021 at 74-75 & Table 3, Ex. 1002, ¶¶ 66-67. It was also known that activity against docetaxel-resistant, castration-resistant prostate cancer had already been observed in patients treated with cabazitaxel. *See*, *e.g.*, Ex. 1002, ¶¶ 66-69, discussing Attard (Ex. 1021). Dr. Sartor speculated that these successes "could be an anomaly," Ex. 1004 at 00188, but the objective responses observed in Mita constituted 25% of treated

prostate cancer patients, a percentage very unlikely to arise from an anomaly. *Id.* at ¶ 225-26. Based on the promising Phase I and II studies, a skilled artisan had good reasons to expect the Phase III study to succeed. Ex. 1002, ¶¶ 120-22.

Further, as explained by Dr. Seth, the Phase III TROPIC study was ***designed to succeed*** because of the choice to compare cabazitaxel to mitoxantrone, which latter treatment the Sartor declaration states had been shown to have ***no clinical benefit***. Ex. 1002 ¶ 223; Ex. 1004 at 00184. Even if clinical data were patentable (it is not), the study described in Winquist and the TROPIC Listing was reasonably likely to succeed. Implementation of the study, including data collection and calculation of the results, was a matter of routine procedure. Ex. 1002, ¶ 172.

X. NO UNEXPECTED RESULTS

Patent Owner has conceded that the specification and prosecution history of the '592 patent concern whether a skilled artisan would have a reasonable likelihood of success, and "not some unexpected property that . . . proves the validity of the claims." Ex. 1035 (cc tr.) at 98:5-99:19 (arguing preamble is limiting because efficacy was used to distinguish prior art), 102:5-103:9 ("So, we're not talking about an unexpected benefit here."). As conceded by Patent Owner, portions of the prosecution history referring to the "unpredictable nature" of clinical studies and "surprising" or "unexpected" results (*e.g.*, Ex. 1004 at 00148-49, 00185, 00093) were strictly related to the success of the Phase III study, not whether treating prostate cancer patients with cabazitaxel had an unexpected property that proves the validity of the claims.

Even if Patent Owner had argued that unexpected results render the claims

valid despite the prior art, this too would fail. To show unexpected results, a comparison must be made between the claimed invention and the closest prior art. *See Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). But the data relied upon during prosecution and in the '592 patent were from a Phase III study (the TROPIC study) comparing cabazitaxel to mitoxantrone, which was not the closest prior art to cabazitaxel. *See, e.g.,* Ex. 1001 at Example 1. As disclosed by Winquist and the TROPIC Listing, the closest prior art was administration of cabazitaxel. No evidence was presented showing any difference in results between the prior art and the claimed invention, nor would any be expected because the ***prior art method is identical to the methods claimed in the '592 patent***.

Even if the method of treatment disclosed in Winquist and the TROPIC Listing were not the closest prior art, an argument for unexpected results would still fail because there are other, closer prior art methods than administration of mitoxantrone. The Patent Owner admitted during prosecution that mitoxantrone had been shown not to improve survival in mCRPC patients. Ex. 1004 at, *e.g.*, 00184. By contrast, the '592 patent admits that docetaxel, a much closer prior art compound than mitoxantrone, was known to provide a survival benefit against mCRPC of 2.4 months. Ex. 1001 1:62-67. This benefit is exactly the same (both in degree and kind) disclosed in the '592 patent specification for cabazitaxel, a close docetaxel analogue. *See id* at 11:35-27; Ex. 1002, ¶ 214. Moreover, the objective response rate in the TROPIC study was very similar to the objective response rate in the Phase II clinical study disclosed in Pivot. *Compare* Ex. 1001 at Table 1 with Ex. 1010 at 1547. Because it was known that cabazitaxel shared docetaxel's anti-

cancer activity and was also active against docetaxel-resistant prostate cancer, Patent Owner has failed to demonstrate that it was unexpected for cabazitaxel to have a similar survival rate in docetaxel-resistant patients as docetaxel had in those patients prior to the onset of docetaxel resistance. *See* Ex. 1002, ¶¶ 213-15.

XI. CONCLUSION

For the reasons set forth above, claims 1-5 and 7-30 of the '592 patent are unpatentable. Petitioners therefore request that an *Inter Partes* Review of these claims be instituted and that these claims be canceled.

Respectfully submitted,

Dated: March 15, 2016

/ Steven W. Parmelee /
Steven W. Parmelee, Lead Counsel
Reg. No. 31,990

XII. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XIII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 8,927,592 to Gupta
1002	Declaration of Dr. Rahul Seth
1003	Curriculum Vitae of Dr. Rahul Seth
1004	File History of 8,927,592 to Gupta
1005	U.S. Provisional Patent Application No. 61/256,160
1006	U.S. Provisional Patent Application No. 61/293,903
1007	U.S. Provisional Patent Application No. 61/355,834
1008	Sanofi-Aventis; XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer (TROPIC). Archived Oct. 23, 2008. https://web.archive.org/web/20081023121613/http://clinicaltrials.gov/ct2/show/NCT00417079 ("the TROPIC Listing").
1009	Winquist *et al.*, Canadian Journal of Urology, 15(1), 2008
1010	Pivot *et al.*, Annals of Oncology 19:1547-1552, 2008
1011	U.S. Patent No. 7,241,907 to Didier *et al.*
1012	Mita *et al.*, Clin Cancer Res, 15(2), 2009
1013	Tannock *et al.*, N. Engl. J. Med. 351, 2004, 1502-1512
1014	3:15-cv-03392 Complaint (D.N.J.)
1015	Booth *et al.*, Nature Reviews Drug Discovery 3, 609-610, 2003
1016	Stedman's Medical Dictionary, 27th Edition (excerpts), 2000
1017	J. S. Abrams *et al.*, 74 Cancer Supp. 1164-1176 (1994)
1018	Kelland *et al.*, Cancer Chemother. Pharmacol. 30, 1992, 444-450

1019	Verweij *et al.*, Annals of Oncology 5, 1994, 495-505
1020	Galletti*, et al.*, *CHEMMEDCHEM*, *2*, 2007, 920-942
1021	Attard, *et al.*, Pathologie Biologie, 54, 2006, 72-84
1022	Beardsley, *et al.*, Curr Opin Support Palliat Care, 2, 2008 161-166
1023	El-Maraghi and Eisenhauer, Journal of Clinical Oncology 26, 1346-1354, 2008
1024	The Taxotere® Label
1025	Liu, Water Insoluble Drug Formulation, First Edition, 525-568, 2000
1026	Affidavit of C. Butler, The Internet Archive
1027	Rosenberg et al., Cancer 110, 556-563, 2007
1028	Gayther et al., Cancer Research 60, 4513-4518, 2000
1029	Ratain and Sargent, European Journal of Cancer 45, 257-280, 2009
1030	Moul, Reviews in Urology 6, S10-S17, 2004
1031	Joint Statement on Claim Construction, 3:15-cv-03392 (D.N.J.)
1032	J. B. Brady Urological Institute Johns Hopkins Medical Institutions, *New Drugs for Prostate Cancer: Chemotherapy Transformed*, 2003
1033	Hospers *et al.*, 14 Current Pharmaceutical Design 3020-3032, 2008
1034	Zhu et al., Cancer Epidemiol. Biomarkers Prev. 15, 3-5, 2006
1035	Markman Hearing Transcript (excerpted), 3:15-cv-03392 (D.N.J.)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,927,592 (and accompanying Exhibits 1001-1035) by overnight courier (Federal Express or UPS), on this 15th day of March, 2016, on the Patent Owner at the correspondence address of the Patent Owner:

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