Trials@uspto.gov
Tel: 571-272-7822

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 IPR2016-00712
Patent 8,927,592 B2

Before BRIAN P. MURPHY, TINA E. HULSE, and
CHRISTOPHER M. KAISER, *Administrative Patent Judges.*

MURPHY, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a); 37 C.F.R. § 42.73(a)

I. INTRODUCTION

Mylan Laboratories Limited ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–5 and 7–30 of U.S. Patent No. 8,927,592 (Ex. 1001, "the '592 patent"). Paper 3 ("Petition" or "Pet."). Petitioner supported its challenge with the Declaration of Dr. Rahul Seth. Ex. 1002. Aventis Pharma S.A. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp."). On September 22, 2016, we instituted an *inter partes* review of claims 1–5 and 7–30 of the '592 patent. Paper 9 ("Institution Decision").

After institution, Patent Owner filed a Response (Paper 21, "PO Resp.") and a Contingent Motion to Amend claims 27–30 of the '592 patent (Paper 22, "MTA"). Patent Owner supported its Response and MTA with the Declaration of Dr. Alton Oliver Sartor (Ex. 2176), the Declaration of Mr. Michael Tate (Ex. 2149), and the Declaration of Mr. Art Lathers (Ex. 2231).

Petitioner filed a Reply (Paper 42, "Reply") and Opposition to Patent Owner's MTA (Paper 43, "MTA Opp."[1]). Petitioner supported its Reply and MTA Opposition with the Reply Declaration of Dr. Seth (Ex. 1043), and the Declaration of Mr. Robert McSorley (Ex. 1044).[2]

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[1] Petitioner filed the MTA Opposition under seal, subject to the Board's ruling on Petitioner's Motion to Seal (Paper 45). Petitioner filed a redacted public version of the MTA Opposition as Paper 44.

[2] Petitioner filed Dr. Seth's Reply Declaration and Mr. McSorley's Declaration under seal, subject to the Board's ruling on Petitioner's Motion to Seal (Paper 45). Petitioner filed redacted public versions of the declarations using the same respective exhibit numbers.

Patent Owner filed a Reply to Petitioner's Opposition to Patent Owner's MTA. Paper 53 ("MTA Reply").[3] Patent Owner supported its MTA Reply with the Reply Declaration of Dr. Sartor (Ex. 2259) and the Declaration of Patricia Matthews, RN, BSN (Ex. 2234).

Patent Owner filed a Motion to Exclude Exhibits 1089–1090 (Paper 61), Petitioner filed an Opposition (Paper 77 (under seal), Paper 78 (public version)), and Patent Owner filed a Reply (Paper 86).

Petitioner filed a Motion to Exclude Exhibits 2170, 2171, and 2179 and certain paragraphs in Exhibits 2001, 2176, and 2149 (Paper 64 (under seal), Paper 68 (public version)), Patent Owner filed an Opposition (Paper 72 (under seal), Paper 73 (public version)), and Petitioner filed a Reply (Paper 89 (under seal), Paper 95 (public version)).

Patent Owner filed Observations (Paper 80) on the cross-examination testimony of Dr. Seth (Ex. 2258) regarding Petitioner's Reply (Paper 42), and Petitioner filed a response to Patent Owner's Observations (Paper 93). Patent Owner also filed Observations (Paper 81 (under seal), Paper 82 (public version)) on the cross-examination testimony of Mr. McSorley (Ex. 2261) regarding Petitioner's Reply (Paper 42), and Petitioner filed a response to Patent Owner's Observations (Paper 92 (under seal), Paper 94 (public version)).

Petitioner filed Observations (Paper 84) on the cross-examination testimony of Dr. Sartor (Ex. 1098) with respect to Patent Owner's MTA, and Patent Owner filed a Response (Paper 90).

[3] Patent Owner filed the MTA Reply under seal, subject to the Board's ruling on Patent Owner's Motion to Seal (Paper 54). Patent Owner filed a redacted public version of the MTA Reply as Paper 52.

An oral hearing was held on June 13, 2017, and a transcript of the oral hearing is of record. Paper 98 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. This is a Final Written Decision under 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73(a) regarding the patentability of the challenged claims. In this case, the claimed treatment method, administering a 20 to 25 mg/m^2 dose of cabazitaxel in combination with prednisone to docetaxel-refractory metastatic prostate cancer patients, was disclosed more than one year before the earliest effective filing date to which the '592 patent might be entitled.[4] Therefore, for the reasons that follow and based on our review of the complete trial record, we determine Petitioner has shown by a preponderance of the evidence that claims 1–5 and 7–30 of the '592 patent are unpatentable. We further determine that Patent Owner's Contingent Motion to Amend claims 27–30 is *denied.*

A. Real Parties in Interest and Related Proceedings

Petitioner identifies (i) Mylan Laboratories Limited, the Petitioner and a wholly-owned subsidiary of Mylan Inc., (ii) Mylan Pharmaceuticals Inc., which is a wholly-owned subsidiary of Mylan Inc., (iii) Mylan Inc., which is an indirectly wholly owned subsidiary of Mylan N.V., and (iv) Mylan N.V. as real parties in interest. Pet. 11.

Patent Owner identifies Patent Owner, Aventis Pharma S.A., Sanofi, the ultimate parent company of Aventis Pharma S.A., and Sanofi-Aventis U.S. LLC, an affiliate of Aventis Pharma S.A., as real parties in interest. Paper 6, 2.

[4] We do not make a determination of the earliest effective filing date, because the references qualify as prior art regardless of that date.

Petitioner and Patent Owner identify the following as related district court proceedings in the District of New Jersey regarding the ’592 patent: *Sanofi-Aventis U.S. LLC v. Mylan Laboratories Limited*, No. 15-03392; *Sanofi-Aventis U.S. LLC v. Apotex Corp*, C. A. No. 15-01835; *Sanofi-Aventis U.S. LLC v. Breckenridge Pharmaceutical, Inc.*, C. A. No. 15-01836; *Sanofi-Aventis U.S. LLC v. Accord Healthcare, Inc.*, C. A. No. 15-02520; *Sanofi-Aventis U.S. LLC v. BPI Labs, LLC*, C. A. No. 15-02521; *Sanofi-Aventis U.S. LLC v. Dr. Reddy Laboratories, Inc*., C. A. No. 15-02522; *Sanofi-Aventis U.S. LLC v. Glenmark Generics Inc.*, C. A. No. 15-02523; *Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC*, C. A. No. 15-02631; *Sanofi-Aventis U.S. LLC v. Actavis LLC*, C. A. No. 15-03107; *Sanofi-Aventis U.S. LLC v. BPI Labs, LLC*, C. A. No. 15-02521. Pet. 12; Paper 6, 2–3.

Petitioner further identifies IPR2016-00627 as an earlier challenge to U.S. Patent No. 5,847,170 directed to the compound cabazitaxel. Pet. 12. We denied institution in IPR2016-00627 (Paper 10) and Petitioner’s request for rehearing (Paper 12).

B. Grounds of Unpatentability

We instituted an *inter partes* review of claims 1–5 and 7–30 of the ’592 patent on the following grounds of unpatentability under 35 U.S.C. § 103:

Reference[s]	Statutory Basis	Challenged Claims
Winquist (Ex. 1009)[5] and TROPIC Listing (Ex. 1008)[6] in view of Attard (Ex. 1021)[7] and Beardsley (Ex. 1022)[8]	§ 103	1, 2, 5, 12, 13, 17–20, 22–25, 27–29
Winquist, TROPIC Listing, and Didier (Ex. 1011)[9]	§ 103	3, 4
Winquist, TROPIC Listing, and Mita (Ex. 1012)[10]	§ 103	7–9
Winquist, TROPIC Listing, and Tannock (Ex. 1013)[11]	§ 103	10, 11, 14, 16

[5] Eric Winquist et al., *Open clinical uro-oncology trials in Canada*, THE CANADIAN JOURNAL OF UROLOGY, 15(1), 3942–49 (February 2008) ("Winquist"). Ex. 1009.

[6] Sanofi-Aventis, *XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer (TROPIC)*, CLINICALTRIALS.GOV (October 23, 2008) ("TROPIC Listing"). Ex. 1008.

[7] Gerhardt Attard et al., *Update on tubulin-binding agents*, PATHOLOGIE BIOLOGIE 54, 72–84 (Elsevier 2006) ("Attard"). Ex. 1021.

[8] Emma K. Beardsley and Kim N. Chi, *Systemic therapy after first-line docetaxel in metastatic castration-resistant prostate cancer*, Curr. Op. SUPPORT PALLIAT. CARE 2, 161–66 (Wolters Kluwer Health 2008) ("Beardsley"). Ex. 1022.

[9] U.S. Patent No. 7,241,907 B2, issued July 10, 2007 to Didier et al. ("Didier"). Ex. 1011.

[10] Alain C. Mita et al., *Phase I and Pharmacokinetic Study of XRP6258 (RPR116258A), a Novel Taxane, Administered as a 1-Hour Infusion Every 3 Weeks in Patients with Advanced Solid Tumors*, CLIN. CANCER RES. 2009:15(2), 723–730 (January 15, 2009) ("Mita"). Ex. 1012.

[11] Ian F. Tannock et al., *Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer*, N. ENGL. J. MED., 351:15, 1502–1512 (October 7, 2004) ("Tannock"). Ex. 1013.

Reference[s]	Statutory Basis	Challenged Claims
Winquist, TROPIC Listing, and Pivot (Ex. 1010)[12]	§ 103	21, 26, 30
Winquist, TROPIC Listing, Pivot, and Tannock	§ 103	15

Paper 9, 22–23.

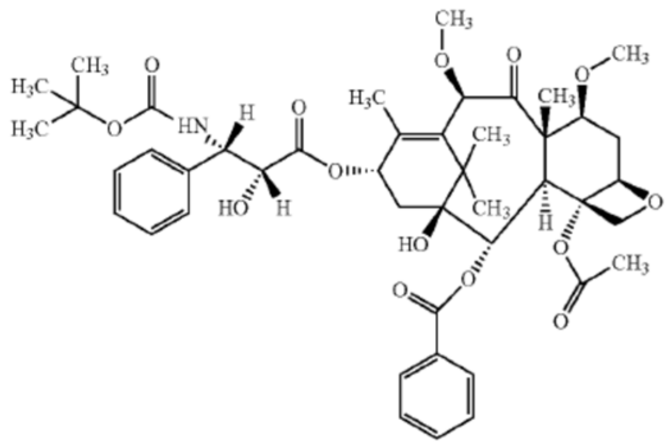
C. The ’592 Patent

The ’592 patent, titled “Antitumoral Use of Cabazitaxel,” issued January 6, 2015, from an application filed April 26, 2012. Ex. 1001. The ’592 patent claims priority through an international application to a series of provisional applications, the earliest of which is dated October 29, 2009. Ex. 1001, (60), (63). The ’592 patent is directed to the use of cabazitaxel in the treatment of prostate cancer, particularly metastatic castration resistant prostate cancer (“mCRPC”). *Id.* at 1:19–26. Because cancer cells may develop resistance to docetaxel (“Taxotere®”[13]), administering cabazitaxel is intended to treat prostate cancer in patients with advanced metastatic disease that has progressed despite previous treatment with a docetaxel-based regimen. *Id.* at 2:61–67. Cabazitaxel is preferably administered in combination with a corticoid, such as prednisone or prednisolone, at a daily dose of 10 mg orally. *Id.* at 3:2–5.

[12] X. Pivot et al., *A multicenter phase II study of XRP6258 administered as a 1-h i.v. infusion every 3 weeks in taxane-resistant metastatic breast cancer patients*, ANNALS OF ONCOLOGY, 19, 1547–1552 (April 23, 2008) (“Pivot”). Ex. 1010.

[13] Taxotere® is the brand name for docetaxel. We also refer to “Taxotere” in this Decision.

The chemical name for cabazitaxel is 4α-acetoxy-2α-benzoyloxy-5β, 20-epoxy-lβ-hydroxy-7β, 10β-dimethoxy-9-oxo-ll-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate. *Id.* at 4:28–31. Cabazitaxel is a taxane compound, the chemical structure of which is shown below:



Id. at 4:8–26. Example 1 of the '592 patent describes a large-scale (phase III) comparative clinical trial of mCRPC patients whose disease had progressed during or after docetaxel treatment, the docetaxel-refractory patients being treated with either 25 mg/m^2 of cabazitaxel or 12 mg/m^2 mitoxantrone, and 10 mg/day of prednisone. *Id.* at 10:30–48. Patients receiving cabazitaxel and prednisone demonstrated a median overall survival that was 2.4 months longer than those receiving mitoxantrone and prednisone. *Id.* at 11:28–37, 11:45–54. The claimed method is directed to administering cabazitaxel and a corticoid to prostate cancer patients whose disease has progressed in spite of previous docetaxel treatment. *Id.* at 5:33–67, 18:54–58, 20:25–30.

D. Challenged Claims

Petitioner challenges claims 1–5 and 7–30 of the '592 patent. Independent claims 1 and 27 are illustrative and are reproduced below:

> 1. 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.

> 27. A method of increasing the survival of a patient with a castration resistant or hormone refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel, comprising administering a dose of 20 to 25 mg/m2 of cabazitaxel, or hydrate or solvate thereof, to the patient in combination with prednisone or prednisolone.

II. ANALYSIS OF THE '592 PATENT CLAIMS

A. Claim Construction

We determine that only the following claim terms require express construction for purposes of this Decision. *See, e.g.*, *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (citation omitted)).

1. Claim 1: "A method for treating a patient"

Petitioner argues that the preamble phrase in claim 1, "a method for treating," is a non-limiting statement of the purpose of the claimed method, or, at most, should be construed as "a method intended to benefit a patient." Pet. 17–19. In its Preliminary Response, Patent Owner opposed Petitioner's proposed construction, arguing that the preamble is limiting and should be construed to mean “a method that produces a therapeutic effect in a patient.” Prelim. Resp. 15–18. In our Institution Decision, we construed “a method for treating a patient” in claim 1 as a non-limiting statement of the purpose of the claimed method. Paper 9, 7–10. At most, the phrase would be construed as “a method intended to benefit a patient.” *Id.* (citing *Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1375–76 (Fed. Cir. 2001) (The preamble language “a method of treating a patient,” “does not result in a manipulative difference in the steps of the claim,” and the recited method steps “are performed the same way regardless [of] whether or not the patient experiences a [therapeutic effect].”)).

Patent Owner’s Response applies the Board’s construction from the Institution Decision and does not argue for a different construction. PO Resp. 14; Reply 1. Therefore, we maintain our construction of the preamble as non-limiting for the reasons given in our Institution Decision. Paper 9, 7–10.

2. Claim 27: “A method of increasing the survival of a patient”

Petitioner argues that the preamble phrase in claim 27, “[a] method of increasing the survival of [a patient],” is a non-limiting statement of the purpose of the claimed method or, at most, should be construed as “a method intended to increase the survival of a patient.” Pet. 19–20. In its Preliminary Response, Patent Owner opposed Petitioner’s proposed construction, arguing that the preamble is limiting and should be construed to mean “a method that prolongs the life of a patient as compared to no treatment or palliative treatment, where that method has been demonstrated to provide a statistically significant increase in overall survival." Prelim. Resp. 19. In our Institution Decision, we construed the preamble in claim 27 as a non-limiting statement of the purpose of the claimed method for the same reasons expressed above regarding "a method for treating a patient" in claim 1. Paper 9, 10. At most, the phrase would be construed as "a method intended to increase the survival of a patient." *Id.*

Patent Owner's Response applies the Board's construction from the Institution Decision and does not argue for a different construction. PO Resp. 14; Reply 1. Therefore, we maintain our construction of the preamble as non-limiting for the reasons given in our Institution Decision. Paper 9, 10.

3. Prosecution History of Independent Claims 1 and 27

A review of the amendments made to independent claims 1 and 27 during prosecution of the '592 patent application provides further context for considering the parties' dispute, discussed in Section II.B., below, over whether a POSA would have had a reasonable expectation of success in achieving the treatment method claimed in the '592 patent.

On April 26, 2012, patent applicant filed proposed independent method of treatment claims 1 and 24 (later amended and issued as claim 27). Ex. 1004 (Part 13), 2397–2402. Claim 1 as originally filed recited:

> 1. A method for treating prostate cancer in a patient in need thereof comprising administering to said patient a compound of formula [cabazitaxel chemical structure] which may be in base form or in the form of a hydrate or a solvate, in combination with prednisone or prednisolone.

Id. at 2397. Dependent claims 8 and 9, which depended directly or indirectly from claim 1, recited administering cabazitaxel at "a dose of between 15 and 25 mg/m^2" and "a dose of 25 mg/m^2, respectively. *Id.* at 2398. Claim 24 as originally filed recited:

> 24. A method of increasing the survival of a patient with hormone refractory metastatic prostate cancer, comprising administering a *clinically proven effective amount* of a compound as defined in claim 1 to the patient in combination with prednisone or prednisolone.

Id. at 2399 (emphasis added). The '592 patent uses lexicography to define "clinically proven" to mean "clinical efficacy results that are sufficient to meet FDA approval standards." Ex. 1001, 4:1–3. The '592 patent further defines "effective amount" to mean "an amount of a pharmaceutical compound, such as cabazitaxel, that produces an effect on the cancer to be treated." *Id.* at 3:65–67.

On March 17, 2014, following an earlier amendment, claim 1 was amended as follows:

> 1. (Currently amended) A method for treating prostate cancer in a patient in need thereof comprising administering to said patient an effective amount of a compound of formula [cabazitaxel chemical structure] which may be in base form or in the form of a hydrate or a solvate, in combination with a corticoid . . . .

Ex. 1004 (Part 2), 280. Patent applicant also added new claims 34, 37, 40, and 43 depending directly or indirectly from claim 1, which recited administering cabazitaxel at "a dose of 25 mg/m^2." *Id.* at 282–83. Claim 24 remained in its original, un-amended form. *Id.* at 282. Patent applicant argued that the claims were patentable over Mita and Tannock, *inter alia*, because the phase III clinical trial results presented in the application (*see* Ex. 1001, Example 1, 10:28–17:33) showed "a statistically significant longer overall survival compared to patients receiving . . . mitoxantrone plus prednisone." Ex. 1004, 285. Patent applicant further argued that Mita's disclosure of a phase I safety and dosing study for cabazitaxel, which showed evidence of anticancer activity at a dose of 25 mg/m^2 in one docetaxel-refractory mCRPC patient, was insufficient to establish a reasonable expectation of "successfully treat[ing]" such patients. *Id.* at 285–86.

The Examiner continued to reject the claims over Beardsley (anticipation under § 102(b)) and Mita, Tannock, and Beardsley (obviousness § 103). *Id.* at 252–268.

On July 10, 2014, applicant's representatives conducted a personal interview with the Examiner. *Id.* at 230. Applicant's representatives presented a draft Rule 132 Declaration by Dr. Sartor, who also attended the interview, to demonstrate "the unpredictability and failure of other taxanes in Phase III clinical trials despite demonstrating efficacy in Phase I and Phase II clinical trials." *Id.* The Examiner agreed that submission of the Rule 132 Declaration and amendments to independent claims 1 and 24 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" would render the claims allowable. *Id.*

On July 16, 2014, patent applicant filed another amendment to application claim 1 (issued claim 1) and claim 24 (issued claim 27) as follows:

> 1. (Currently Amended) A method for treating ~~prostate cancer in~~ a patient <u>with prostate cancer that has progressed</u>

> during or after treatment with docetaxel, ~~in need thereof~~ comprising administering to said patient a dose of 20 to 25 mg/m^2 of cabazitaxel, or a hydrate or solvate thereof, ~~an effective amount of a compound of formula [cabazitaxel chemical structure] which may be in base form or in the form of a hydrate or a solvate,~~ in combination with a corticoid.
>
> 24. (Currently Amended) A method of increasing the survival of a patient with a castration resistant or hormone refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel, comprising administering a ~~clinically proven effective amount~~ dose of 20 to 25 mg/m^2 of cabazitaxel, or hydrate or solvate thereof, ~~a compound as defined in claim 1~~ to the patient in combination with prednisone or prednisolone.

Ex. 1004 (Part 1), 138, 140.

In claim 1, patent applicant deleted "in need thereof" in the preamble (*id.* at 138), a phrase Patent Owner adds to the body of proposed substitute claim 31 in the MTA (MTA, 27). Patent applicant also deleted "an effective amount" from the body of claim 1 and replaced it with "a dose of 20 to 25 mg/m^2" of cabazitaxel. Ex. 1004 (Part 1), 138. Similarly, in claim 24, patent applicant deleted "clinically proven effective amount" and replaced it with a "dose of 20 to 25 mg/m^2" of cabazitaxel**.** *Id.* at 140. The deletions removed the lexicographically-defined limitations of producing "an effect on the cancer to be treated" ("effective amount" in clam 1) and achieving "clinical efficacy results that are sufficient to meet FDA approval standards" ("clinically proven effective amount" in claim 24), respectively, and replaced them with a 20 to 25 mg/m^2 dosage range. Ex. 1001, 3:65–4:3, 10:47–48, 11:1–13:66, 17:31–18:29, Figs. 1–7.

In remarks, patent applicant 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. Ex. 1004 (Part 1), 145 ("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."); *id.* at 148 ("the doses of cabazitaxel and prednisone are not disclosed [in Beardsley]"). Patent applicant further argued that the cited art was insufficient to justify a reasonable expectation that the claimed method "would successfully treat prostate cancer." *Id.* at 147. A Notice of Allowance ensued. *Id*. at 91–94. The Examiner was persuaded by patent applicant's arguments and evidence, particularly Dr. Sartor's Rule 132 Declaration statements that the prior art, while disclosing "promising early clinical results, . . . failed to predict whether therapies would ultimately provide a clinically meaningful benefit to the desired patient populations and that mCRPC was known to be a particularly challenging and unpredictable indication." *Id.* at 93.

As indicated by patent applicant's final claim language, achieving a clinically effective treatment is not a limitation of the '592 method claims. *See Bristol-Myers Squibb Co.*, 246 F.3d at 1375 ("The express dosage amounts are material claim limitations; the statement of the intended result of administering those amounts [an antineoplastically effective amount] does not change those amounts or otherwise limit the claim."); *see also id.* at 1376 ("We therefore affirm the district court's interpretation of claims 5 and 8 as limited only to the actual steps of those claims, without regard to the result of performing the claimed steps" [to effect regression of a taxolsensitive tumor]). In sum, the independent method claims of the ’592 patent are limited to the step(s) of:

- administering a 20–25 mg/m^2 dose of cabazitaxel (or its hydrate or solvate);
- in combination with a corticoid (claim 1), such as prednisone or prednisolone (claim 27);
- to a docetaxel-refractory prostate cancer patient (claim 1); or
- to a docetaxel-refractory mCRPC patient (claim 27).

The recited method steps, although they must have utility, are performed without regard to whether the claimed method results in a clinically effective treatment.

B. Ground 1: Asserted Obviousness of Claims 1, 2, 5, 12, 13, 17–20, 22–25, and 27–29 over Winquist and the TROPIC Listing in View of Attard and Beardsley

Petitioner asserts that the subject matter of claims 1, 2, 5, 12, 13, 17–20, 22–25, and 27–29 of the ’592 patent would have been obvious to a person of ordinary skill in the art (hereafter “POSA”) based on the combined teachings of Winquist and the TROPIC Listing in view of the knowledge of a POSA.[14] Pet. 25–38. Winquist and the TROPIC Listing together disclose

[14] The parties provide largely similar descriptions of a POSA. *Compare* Pet. 9–10 *with* PO Resp. 14. Patent Owner acknowledges that any differences should not affect the outcome of this case. PO Resp. 14; Reply 1. We agree. For purposes of this decision, we adopt and apply Patent Owner’s description of a POSA as an oncologist or medical doctor specializing in oncology who would have had experience in the treatment of prostate cancer, including metastatic prostate cancer, in evaluating therapies for prostate cancer, and who would have had access to information regarding pharmacokinetics and mechanisms of drug resistance. PO Resp. 14 (citing

the same treatment protocol described in Example 1 of the ’592 patent (“the TROPIC Study”), more than one year before the earliest effective priority date to which the ’592 patent may be entitled (October 29, 2009). Pet. 1–2, 6–7 (citing Ex. 1008; Ex. 1009), 25–27 (citing Ex. 1002 ¶¶ 115–121); Ex. 1001, (60), 10:30–48. In our Institution Decision, we amended the ground to add “in view of Attard and Beardsley,” two prior art references cited and discussed by Petitioner that reflect the knowledge of a POSA. Paper 9, 16 (citing *SightSound Techs., LLC v. Apple Inc.*, 809 F.3d 1307, 1312–13 (Fed. Cir. 2015) (noting that governing statutory provisions do not limit the Board’s authority to proceed with AIA trial proceedings only on the specific statutory grounds alleged in the petition)).

Patent Owner does not dispute that Winquist and the TROPIC Listing are prior art under 35 U.S.C. § 102(b) (pre-AIA). PO Resp. 37–41. Patent Owner’s Response to the Petition asserts that a POSA would not have had a reasonable expectation of successfully treating docetaxel-refractory prostate cancer patients with cabazitaxel. PO Resp. 16–43. Patent Owner further asserts that evidence of secondary considerations supports the non-obviousness of the challenged ’592 patent claims. *Id.* at 50–56. We address the parties’ arguments below.

1. Winquist

Winquist is a February 2008 disclosure of open, uro-oncology clinical trials in Canada that qualifies as prior art under 35 U.S.C. § 102(b) (pre-AIA). Ex. 1009, 3942. The format of each entry is the same; a descriptive

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Ex. 2176 ¶ 28). We also rely on the cited references as reflecting the level of ordinary skill in the art at the time of the claimed invention. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

title of the clinical trial followed by an identification of the trial and the entity coordinating it, the trial design, patient population, sample size, and primary endpoint. *Id.* Winquist discloses a randomized phase III clinical trial coordinated by Sanofi-Aventis involving treatment of mCRPC patients previously treated with docetaxel (the TROPIC Study). *Id.* at 3948.

Significantly, and unlike the prior art considered by the Examiner during prosecution, Winquist discloses the administration of a 25 mg/m^2 dose of cabazitaxel to mCRPC patients: "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." *Id.* The primary endpoint is overall survival. *Id.*

With regard to independent claims 1 and 27 of the '592 patent, Winquist does not disclose expressly that the prostate cancer "has progressed during or after treatment with docetaxel" (*id.*; Pet. 25–26), but Petitioner contends that progression after treatment with docetaxel was implicit and would have been understood by a POSA. Pet. 25–26 (citing Ex. 1002 ¶¶ 65, 94 (95), 117).

2. The TROPIC Listing

The TROPIC Listing was published in the ClinicalTrials.gov database of the National Library of Medicine, and it was archived by The Internet Archive on October 23, 2008. Ex. 1026, Ex. A. The TROPIC Listing also qualifies as prior art under 35 U.S.C. § 102(b). The TROPIC Listing discloses the same phase III clinical trial reported in Winquist (the Sanofi-Aventis TROPIC Study), 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, 1; Ex. 1002 ¶¶ 118–120. The TROPIC Listing, like Winquist, discloses that cabazitaxel is to be administered every three weeks and that expected patient enrollment is 720 patients. Ex. 1008, 1–2; Ex. 1009, 3948. The TROPIC Listing expressly states 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," after previous treatment with docetaxel. Ex. 1008, 2. The primary outcome, as also reported in Winquist, is overall survival. *Id*. at 1; Ex. 1009. The TROPIC Listing notes the start date of the clinical trial was December 2006. Ex. 1008, 2.

With regard to independent claims 1 and 27 in the '592 patent, the TROPIC Listing, unlike Winquist, does not disclose an administration dose of cabazitaxel. *Id.*; Pet. 7.

3. Attard and Beardsley

Attard is a review article reporting, *inter alia*, on a phase I dosing study for cabazitaxel, which was originally reported in Mita (Ex. 1012). Ex. 1021, 75 (Col. 1 ¶ 2 n.23). Mita discloses administration of a 15 mg/m^2 dose to one prostate cancer patient and a 25 mg/m^2 dose to a docetaxel-refractory metastatic prostate cancer patient. Ex. 1012, 727 (Col. 1 ¶ 2). Attard reports that Mita's phase I cabazitaxel study showed two objective responses in CRPC patients, and noted that one of the patients was docetaxel refractory (25 mg/m^2 dose). Ex. 1021, 75 (Col. 1 ¶ 2 n.23). Attard also describes cabazitaxel (XRP6258) as showing improvement over paclitaxel and docetaxel with “higher therapeutic indices” and “activity against resistant tumours.” *Id.* at 74.

Beardsley reports on a phase II clinical trial of cabazitaxel administered to docetaxel-resistant metastatic breast cancer patients, which was originally reported in Pivot (Ex. 1010). Ex. 1022, 163 (Col. 2 ¶¶ 4–5). Pivot administered an initial cabazitaxel dose of 20 mg/m^2, then escalated the dose to 25 mg/m^2 in patients who did not experience a significant adverse event during the first treatment cycle. Ex. 1010, 1548 (Col. 2 ¶ 3). Beardsley reports that the objective response rate to cabazitaxel treatment in docetaxel-refractory metastatic breast cancer patients was 14% in the Pivot study. Ex. 1022, 163 (Col. 2 ¶ 4). Beardsley further reports that while a phase II clinical trial with cabazitaxel had not been performed in CRPC patients, “given its activity in the docetaxel refractory setting described above, this agent is currently being investigated in a phase III multi-center, randomized superiority trial comparing 3-weekly XRP6258 with prednisone to mitoxantrone with prednisone in patients with castrat[ion] resistant metastatic prostate cancer previously treated with docetaxel-containing treatment.” *Id.* (Col. 2 ¶ 5).

4. Analysis of Independent Claims 1 and 27

A claimed invention is unpatentable if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. 35 U.S.C. § 103(a). Obviousness under 35 U.S.C. § 103 requires an assessment of (1) the “level of ordinary skill in the pertinent art,” (2) the "scope and content of the prior art," (3) the "differences between the prior art and the claims at issue," and (4) "secondary considerations" of nonobviousness such as "commercial success, long-felt but unsolved needs, failure of others, etc." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)). A party who petitions the Board for a determination of obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)). We assess Petitioner's evidence and argument, weighed against Patent Owner's evidence and argument, according to the standard articulated above.

a. Winquist and the TROPIC Listing disclose all method step limitations

As stated previously, the independent method claims of the '592 patent are limited to the step(s) of:

- administering a 20–25 mg/m^2 dose of cabazitaxel (or its hydrate or solvate);
- in combination with a corticoid (claim 1), such as prednisone or prednisolone (claim 27);
- to a docetaxel-refractory prostate cancer patient (claim 1) or a docetaxel-refractory mCRPC patient (claim 27).

Winquist discloses the same treatment protocol as the Sanofi-Aventis TROPIC Study, also described in Example 1 of the '592 patent, namely administering a 25 mg/m^2 dose of cabazitaxel in combination with prednisone every three weeks to mCRPC patients previously treated with docetaxel. Ex. 1009; Ex. 1001, 10:30–48. The TROPIC Listing describes the same TROPIC Study protocol and discloses the only limitation of claims 1 and 27 arguably not expressly disclosed in Winquist, that a patient's prostate cancer "has progressed during or after treatment with docetaxel." Ex. 1008, 2 ("Documented progression of disease" after previous treatment with a docetaxel-containing regimen); Pet. 26–27 (citing Ex. 1002 ¶¶ 118–121). We also credit Dr. Seth's testimony that a POSA, an oncologist experienced in treating mCRPC, would have understood Winquist as disclosing treatment of mCRPC patients who experienced disease progression during or after docetaxel treatment, because if the previous docetaxel treatment had stopped the cancer from progressing, second-line treatment with cabazitaxel would be unnecessary. Ex. 1002 ¶ 117.

Dr. Sartor testified that Winquist and TROPIC Listing expressly teach administration of the recited 25 mg/m^2 dose of cabazitaxel in docetaxel-resistant mCRPC patients as a new cycle every three weeks, in combination with prednisone. Ex. 1041, 62:8–18, 73:10–15, 96:17–22, 150:6–152:6. Dr. Sartor also testified that Winquist and the TROPIC Listing disclosed a treatment regimen for mCRPC patients that had progressed during or after treatment with docetaxel. Ex. 1041, 59:7–20, 65:2–18, 67:23–68:6, 83:10–15, 87:13–88:4, 93:9–17. Patent Owner does not contend otherwise. PO Resp. 37–41. Petitioner also provides a claim chart identifying where each recited limitation is disclosed in Winquist and the TROPIC Listing. Pet. 35–38.

Therefore, we find Petitioner has established by a preponderance of the evidence that Winquist and the TROPIC Listing disclose all of the method steps recited in independent claims 1 and 27 of the '592 patent.

b. Motivation to combine

A preponderance of the evidence establishes that a POSA would have had good reason to combine the teachings of Winquist and the TROPIC Listing and would have read the two references together. Pet. 26–27 (citing Ex. 1002 ¶¶ 118–120). Winquist and the TROPIC Listing disclose the same treatment method being used in the same clinical trial for treating the same patient population – the Sanofi-Aventis TROPIC Study. *Id.* Petitioner relies on Attard and Dr. Seth's Declaration testimony for the proposition that "it was known in the art that anticancer activity against docetaxel-resistant, castration-resistant prostate cancer was observed in patients treated with cabazitaxel," further reinforcing a POSA's understanding that Winquist and the TROPIC Listing should be read together as administering 25 mg/m^2 cabazitaxel (and prednisone) to treat the same docetaxel-refractory mCRPC patient population. Pet. 27 (citing Ex. 1002 ¶¶ 66–69; Ex. 1021, 74–75 (Table 3)). Beardsley also makes reference to Pivot's phase II clinical study of cabazitaxel among docetaxel-refractory metastatic breast cancer patients as providing motivation for the TROPIC Study, further reinforcing the point. *Id.* at 28 (citing Ex. 1002 ¶¶ 70–72; Ex. 1022, 163). As Dr. Seth testifies:

> By 2008, cabazitaxel had been validated by both Phase I and Phase II clinical studies as a drug to treat metastatic cancers, including docetaxel-resistant cancers. It was known that a Phase III trial was underway administering cabazitaxel with prednisone for treating castration-resistant metastatic prostate cancer that had previously been treated with docetaxel.

Ex. 1002 ¶ 70. Petitioner's cited evidence is highly persuasive that a POSA in 2008 would have known that Winquist and the TROPIC Listing disclosed the same ongoing phase III clinical trial – the TROPIC Study – and would have read the two references together.

Dr. Sartor, Patent Owner's expert, confirmed that Winquist and the TROPIC Listing describe the same treatment regimen actually being used in the TROPIC Study and that a POSA would have read the two references together. Ex. 1041, 57:2–8, 94:14–95:4, 97:5–100:4. Patent Owner implicitly acknowledges the sufficiency of Petitioner's evidence establishing a motivation to combine the teachings of Winquist and the TROPIC Listing. *Compare* PO Resp. 16–46, *with* PO Resp. 47–49. Therefore, we are satisfied that Petitioner has established by a preponderance of the evidence that a POSA in 2008 would have combined the teachings of Winquist and the TROPIC Listing and read the two references together.

c. Reasonable expectation of success in achieving the claimed method of treatment

The fundamental dispute between Petitioner and Patent Owner concerns the relevant standard for evaluating whether a POSA would have had a reasonable expectation of "success" in achieving the claimed method. It devolves into a claim construction dispute. Unlike the prior art before the Examiner during prosecution of the '592 patent claims, Winquist expressly discloses the same 25 mg/m^2 dose of cabazitaxel for treating docetaxel-refractory mCRPC patients described in Example 1 of the '592 patent. This is not surprising given that Winquist discloses the same TROPIC Study treatment protocol. Faced with this evidence, Patent Owner attempts to raise the bar for the standard of "success" required to prove obviousness of the claimed method. We are not persuaded by Patent Owner's argument and evidence.

i) Relevant standard for "success"

Petitioner contends a POSA reasonably would have concluded from Winquist and the TROPIC Listing, in view of the knowledge of a POSA, that a 25 mg/m^2 dose of cabazitaxel administered with prednisone every three weeks would have anti-cancer activity in docetaxel-refractory mCRPC patients. Pet. 27–29 (citing Ex. 1002 ¶¶ 66–72, 120–122). Thus, evidence of anti-cancer activity in the target patient population – not clinical efficacy – equates to "success" in Petitioner's analysis. Petitioner also argues that absolute predictability is not required. *Id.* at 29 (citing *Pfizer*, 480 F.3d at 1364; *In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988)). Petitioner further emphasizes that the "method for treating" preamble in claim 1 and the "method of increasing the survival" preamble in claim 27 are not claim limitations. *Id.* at 17–20, 29, 33. We agree the preambles are not limiting, as stated in our claim construction analysis in Section II.A., above.

Patent Owner contends that while "predictability is a touchstone of obviousness," predictability "refers not only to the expectation that the prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose." PO Resp. 15 (citing *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009); also citing *In re Cyclobenzaprine,* 676 F.3d 1063, 1071–72 (Fed. Cir. 2012) (disclosure of PK values insufficient without a showing that a POSA would reasonably expect those values to yield a therapeutically effective formulation)). Based on this premise, Patent Owner argues that Petitioner does not address "the surprise in the field" or the risks of cabazitaxel therapy, and that Petitioner's evidence is insufficient to have allowed a POSA to reasonably expect that cabazitaxel's clinical benefit in docetaxel-refractory mCRPC patients would outweigh the risks of such treatment. PO Resp. 17–19. Patent Owner defines "success" in the context of the '592 patent claims as "a treatment for prostate cancer that provides a clinical benefit in patients previously treated with docetaxel, where the side effects of that treatment are not such that administering it would be inappropriate for those patients notwithstanding the benefit." *Id.* at 20.

Petitioner replies that the '592 patent claims do not recite a treatment method that has achieved (i) FDA approval (a "clinically proven" treatment as defined in the '592 patent specification (Ex. 1001, 4:1–3)), (ii) a successful phase III trial, or iii) an actual increase in survival of a patient. Reply 1. Petitioner further argues that, because the '592 patent claims "do not recite a required result regarding efficacy or safety, Petitioner need not establish a reasonable likelihood of a successful phase III trial or FDA approval to demonstrate obviousness." *Id.* at 3. We agree.

Patent Owner's argument is misplaced because it implicitly defines "success" as a clinically effective treatment where clinical benefit outweighs potential risks to the patient in the context of a phase III clinical trial designed for FDA approval. As we explained in our claim construction analysis, the '592 patent claims are not limited to a clinically effective treatment. A close examination of the legal foundation of Patent Owner's argument reveals significant fault lines.

DePuy Spine involved the question of whether a hypothetical medical device claim to a pedicle screw for stabilizing spinal column segments would have been obvious over a combination of prior art references. *DePuy Spine*, 567 F.3d at 1324–25. The issue was raised in the context of defendant's ensnarement defense to patent owner's allegation of infringement under the doctrine of equivalents. *Id.* The Federal Circuit's consideration of whether prior art mechanical elements would have been combinable to achieve the hypothetically claimed pedicle screw, and whether such a prior art device would have worked for its intended purpose of stabilizing spinal column segments, has little bearing on the method of treatment claims at issue in the present case. *DePuy Spine*, moreover, involved a prior art teaching away that would have rendered the proposed combination inoperative. *See* Reply 2 (citing *DePuy Spine*, 567 F.3d at 1326–27). Here, there is a clear motivation to combine Winquist and the TROPIC Listing because the references describe the same clinical study, administering 25 mg/m^2 of cabazitaxel in combination with prednisone every 3 weeks to the same patient population, which was also referenced in Beardsley. Unlike the *DePuy Spine* case, there is no evidence of a teaching away from the asserted combination of Winquist and the TROPIC Listing.

In re Cyclobenzaprine also is distinguishable because the patent in that case specifically recited a method that "provides [a] therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions." 676 F.3d at 1066. The Federal Circuit reversed the district court's determination of obviousness because the prior art did not teach sufficiently "whether any particular PK profile . . . would produce a therapeutically effective formulation." *Id.* at 1070; *see also Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1303 (Fed. Cir. 2006) ("A therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification.”). Here, in contrast to *In re Cyclobenzaprine* and *Amgen*, the ’592 patent does not recite a comparable “therapeutically effective” limitation, and Winquist does disclose administration of the recited 25 mg/m^2 dose of cabazitaxel in combination with prednisone to mCRPC patients previously treated with docetaxel.

The appropriate test for obviousness requires “a motivation to combine accompanied by a reasonable expectation of achieving what is claimed in the patent-at-issue.” *Intelligent Bio-Systems Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). In *Intelligent Bio-Systems*, the Federal Circuit underscored the importance of considering “the appropriate scope of the patent’s *claimed invention* in evaluating the reasonable expectation of success.” 821 F.3d at 1367. Consistent with the claim amendments made by the ’592 patent applicant during prosecution, the claims at issue here do not recite an FDA-approved clinically effective treatment. Reply 6–7. As stated above, the claims were amended to replace limitations reciting an “effective amount” (claim 1) and a “clinically proven effective amount” (claim 27) with a recited dosage range of 20 to 25 mg/m^2 of cabazitaxel. Ex. 1004 (Part 1), 138, 140. There is no recitation in the ’592 patent claims of administering a therapeutically effective amount of cabazitaxel in combination with prednisone or a comparable recitation requiring a particular therapeutic effect, clinical benefit, or result. Reply 6–7 (distinguishing *Coal. For Affordable Drugs V LLC v. Biogen MA Inc.*, Case IPR2015-01136, slip op. at 9-10 (PTAB Sept. 2, 2015) (Paper 23)). Petitioner, therefore, need not establish a POSA reasonably would have expected successful phase III clinical trial results, FDA approval of cabazitaxel and prednisone combination therapy, or an actual increase in patient survival, to demonstrate obviousness of claims 1 and 27. *Id.* at 3 (citing *In re Montgomery*, 677 F.3d, 1375, 1380 (Fed. Cir. 2012) (claims to a method for treating or preventing a stroke do not create "an efficacy requirement"); *Intelligent Bio-Systems*, 1367–68 (quantitative removal irrelevant to reasonable expectation because not a claim requirement)); *see also id.* at 7 (citing *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) ("There is no requirement that one of ordinary skill have a reasonable expectation of success in developing Combigan®. Rather, the person of ordinary skill need only have a reasonable expectation of success of developing the claimed invention."); *Astrazeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1064–65 (Fed. Cir. 2010) (lacking FDA approval does not demonstrate lack of drug utility)).

Patent Owner further contends that Winquist and the TROPIC Listing cannot render unpatentable the claims of the '592 patent because "disclosure of a protocol for testing a hypothesis without any evidence of efficacy or safety is insufficient to show that the method itself is useful for the claimed patients." PO Resp. 37 (citing *Biogen*, Case IPR2015-01136, slip op. at 9–10 (PTAB Sept. 2, 2015) (Paper 23)). To the contrary, not only did the *Biogen* decision acknowledge that it would be inappropriate to engraft an efficacy or FDA approval requirement onto the obviousness analysis, *Biogen* is distinguishable because the prior art failed to disclose the "therapeutically effective amount" limitation recited in the method of treatment claims at issue. *Biogen*, IPR2015-01136, 6–7.[15]

For the reasons given above, we determine that a reasonable expectation of success in the context of the '592 patent claims may be satisfied by evidence that a POSA reasonably would have expected a 25 mg/m^2 dose of cabazitaxel in combination with prednisone, as disclosed in Winquist and the TROPIC Listing, to have anti-cancer activity in docetaxel-refractory mCRPC patients.

ii) A preponderance of the evidence supports finding a reasonable expectation of success

Petitioner has established by a preponderance of the evidence that a POSA would have had a reasonable expectation of successfully achieving the claimed treatment method based upon the teachings of Winquist and the TROPIC Listing, in view of Attard, Beardsley, and the knowledge of a POSA. Winquist teaches administration of a 25 mg/m^2 dose of cabazitaxel in combination with prednisone, the same 25 mg/m^2 dose taught by Mita as exhibiting "anti-cancer activity" when administering cabazitaxel to a docetaxel-refractory metastatic prostate cancer patient. Ex. 1012, 727 (Col. 1 ¶ 2). Mita notes a significant decrease in prostate-specific antigen and a "confirmed partial response" in the docetaxel-refractory patient, two of the same measures reported in the analysis of the TROPIC Study in the '592 patent. Ex. 1001, 11:8–9, 11:26–64. Dr. Seth explains that the RECIST guidelines define a partial response as a reduction of the largest diameter of

[15] We further note the *Biogen* decision is not precedential and, therefore, not binding on this panel.

the cancerous lesion by at least 30%. Ex. 1002 ¶¶ 27, 69; Ex. 1043 ¶ 15; Ex. 1051, 983–84. Attard reports favorably on the Mita study and teaches a POSA that cabazitaxel shows improvement over paclitaxel and docetaxel as evidenced by higher therapeutic indices and "activity against [taxane] resistant tumors." Ex. 1021, 74–75.

Petitioner further emphasizes that in 2008 a POSA would have known (i) anti-cancer activity had been observed in a docetaxel-refractory mCRPC patient treated with cabazitaxel (Attard, Ex. 1021, 75/Mita, Ex. 1012, 727), (ii) the safety profile of cabazitaxel was "very favorable" compared to paclitaxel and docetaxel (Pivot, Ex. 1010, 1551), (iii) cabazitaxel was known to target the same tubulin binding site as docetaxel, shown to be effective in breast and prostate cancers (Attard, Ex. 1021, 74–75), (iv) cabazitaxel's 14% objective response rate in docetaxel-refractory metastatic breast cancer patients was a motivation for carrying out the phase III clinical trial in mCRPC patients previously treated with docetaxel (Beardsley, Ex. 1022, 163/Pivot, Ex. 1010, 1550), and (v) assessing overall survival was the "primary endpoint" of the TROPIC Study reported in Winquist and the TROPIC Listing (Winquist, Ex. 1009, 3948/TROPIC Listing, Ex. 1008, 1). Pet. 27–28, 33–34 (citing Ex. 1002 ¶¶ 66–72, 110, 132, 222; Ex. 1008, 1; Ex. 1009, 3948; Ex. 1010, 1548, 1551; Ex. 1021, 72, 74–75, Table 3; Ex. 1022, 163). Winquist also taught a POSA that, as of October 23, 2008, the phase III TROPIC Study had been ongoing since December 2006, a favorable indicator according to Dr. Seth. Ex. 1002 ¶ 122. Dr. Seth concludes that, based on the available knowledge regarding administration of cabazitaxel in docetaxel-resistant prostate and breast cancer patients, described above, a POSA – a clinical oncologist with experience treating mCRPC patients and knowledge of drug resistance mechanisms – would have reasonably concluded that the treatment method disclosed in Winquist and the TROPIC Listing "would yield intrinsic anti-cancer activity, and would produce therapeutic or other medical benefits similar to those for which docetaxel had been previously administered—for example, an increase in overall survival." *Id.* ¶¶ 120–121; *see also* Reply 28 (citing Ex. 1008, 1–2; Ex. 1009, 3948).

Patent Owner contests Petitioner's reasonable expectation of success arguments and evidence. PO Resp. 16–46. However, Patent Owner's argument and evidence regarding the alleged surprise in the field, risks of administering cabazitaxel, and unpredictability of the clinical trial results from the TROPIC Study, including whether those clinical results would be sufficient for FDA approval, are based on a legally irrelevant standard of "success" to the extent Patent Owner implies that "success" requires achieving clinical trial results sufficient for FDA approval. Patent Owner's analysis also effectively excludes Winquist and the TROPIC Listing as prior art. Examples abound.

Patent Owner's evidence that Dr. Sartor was "surprised when he reviewed the *data*" from the TROPIC Study for the first time, as were others when he "presented the *results* publicly," and that "prediction of a *positive phase III study* was 'an impossible endeavor,'" speaks to therapeutic efficacy proven by statistically significant data taken from successful phase III clinical trial results needed for FDA approval. PO Resp. 16 (emphases added) (citing Ex. 2004, 1711 (Col. 1 ¶ 2); Ex. 2176 ¶¶ 93, 185, 187). Providing statistically significant data and results to establish a clinically effective treatment for FDA approval is neither a requirement of the '592 patent claims nor the appropriate measure of success. Therefore, such evidence is entitled to little weight.

Further undercutting Patent Owner's argument, Dr. Sartor admitted that he incorrectly concluded that Winquist and the TROPIC Listing are not prior art:

> Q. The TROPIC listing is one of the pieces of prior art that you viewed as appropriate to consider in evaluating the validity of the 592 patent; is that correct?
> A. I didn't think it was prior art when you just put it in a listing. It's not relevant to me to put it in a listing. So I didn't -- I honestly don't think that's part of the prior art when you list a clinical trial. What does that mean? It means nothing.
>
> Q. When you were reaching your opinions in this proceeding regarding the validity of the 592 patent, is it correct that you did not evaluate the TROPIC listing as a prior art reference?
> A. I didn't really care if they listed it or not. It was irrelevant to my opinion. . . .
>
> Q. With that understanding, when you reached your opinions in this case, in this proceeding, did you understand that the TROPIC listing was prior art to the 592 patent?
> A. I don't think it is. I think it's just a listing. That listing had no relevance to my opinion whatsoever, and I was very surprised that someone who's an oncologist would say so. I mean I was actually kind of shocked. So I wouldn't call it the prior art. I'd just call it a listing.

Ex. 1041, 43:18–45:11 (objections to form omitted). With regard to Winquist, which disclosed administering 25 mg/m^2 of cabazitaxel in combination with prednisone to treat docetaxel-refractory mCRPC patients, and Pivot, which disclosed administering 20–25 mg/m^2 of cabazitaxel to treat docetaxel-refractory metastatic breast cancer patients, Dr. Sartor testified as follows:

> Q. When you reached your opinions in this proceeding, did you understand that the Winquist reference is prior art to the 592 patent?
> A. Not in my mind. In somebody else's mind.
>
> Q. When you reached your opinions in this proceeding, did you have an understanding of the Pivot reference as prior art to the 592 patent?
> A. It was alleged to be a portion of the prior art. And I think that that was a debatable issue.

Id. at 45:12–24 (objections to form omitted).

Dr. Sartor's analysis is undermined by his apparent dismissal of highly relevant clinical trial listings as prior art. *See Montgomery*, 677 F.3d at 1378–80 (published protocol for ongoing phase III study was prior art that anticipated claims). Thus, we give little weight to Patent Owner's cited evidence regarding the asserted surprise in the field and Dr. Sartor's opinion that a POSA would not have had a reasonable expectation of successful treatment in a phase III clinical trial from reading Winquist and the TROPIC Listing in view of Attard (reporting on the Mita study) and Beardsley (reporting on the Pivot study). *See* PO Resp. 21–43 (citing, *inter alia*, Ex. 2176 ¶¶ 45 (a POSA "would need clinical data showing that the medicine provides a specific clinical benefit to the patient, such as those described in the specification of the '592 patent"), 101 ("The multiple failed phase III studies discussed above . . . demonstrate the unpredictability in the art and that a POSA would ***not*** have had a reasonable expectation of success."), 110–111 ("In the context of initiating a phase III study . . . [a] POSA reviewing Attard and Mita, alone or in combination . . . would have been left with great uncertainty as to whether cabazitaxel in combination with a corticoid would be a successful treatment for prostate cancer patients worsening during or after docetaxel."), 133 ("Pivot, an open-label, single-arm study, with no data from previous phase II studies . . . would not provide a POSA with a reasonable expectation of success in a phase III trial in a different cancer type."), 171 ("a POSA would not have reasonably expected success for cabazitaxel in prostate cancer simply based on the fact that Sanofi was performing the TROPIC study."). Dr. Sartor's opinions rely on Patent Owner's incorrect standard for "success" and a misconception regarding the relevant prior art.

Patent Owner also asserts that in view of the risks associated with cabazitaxel therapy:

> Mylan, at minimum, needs to demonstrate that a POSA would have had a reasonable expectation that administering 20-25 mg/m^2 of cabazitaxel in combination with a corticoid to the claimed patients was efficacious and that the regimen's efficacy outweighed the harm to those patients. That is, Mylan's references needed to show that there was a reasonable expectation that administering 20-25 mg/m^2 of cabazitaxel in combination with a corticoid to the claimed patients would be *sufficiently safe and effective to be useful to physicians as a treatment for prostate cancer worsening after docetaxel*.

Id. at 18 (emphasis added). According to Petitioner, governing precedent is to the contrary and provides that the standard for proving obviousness is lower than the standard for proving efficacy and safety sufficient to warrant FDA approval. Reply 7 (citing *Allergan*, 726 F.3d at 1292 ("Motivation to combine . . . cannot be limited to those reasons the FDA sees fit to consider in approving drug applications."); *Astrazeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1064–65 (Fed. Cir. 2010) (lacking FDA approval does not demonstrate lack of drug utility)). Moreover, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364.

Patent Owner cites Dr. Seth's deposition testimony for the proposition that Mita and Pivot were not designed to assess the efficacy and risks associated with administration of cabazitaxel, and that more data from a larger clinical study was needed "for a POSA to determine if cabazitaxel would be sufficiently effective in the claimed patients such that the potential benefit would outweigh the harm." PO Resp. 18–20. First, Patent Owner's proposed standard engrafts inappropriate safety and efficacy constraints onto the utility of the claimed method as a measure of "success." *See Bristol-Myers Squibb*, 246 F.3d at 1378 ("the claims only require the administration of specific amounts of [the compound recited in the challenged claims] and not the achievement of a particular result."). Second, as explained by Dr. Seth, the reported incidences of neutropenia and other side effects of cabazitaxel were not so high as to require a proven survival benefit as a treatment prerequisite. Ex. 1043 ¶ 26; Ex. 1012, 726 (Table 3); Ex. 1010, 1550–51. Therefore, we give little weight to Patent Owner's evidence and argument regarding the necessity to weigh the potential clinical benefits against the risks of cabazitaxel administration (diarrhea, nausea, fatigue, neutropenia, and sensory neuropathy), particularly when the prior art discloses the claimed treatment method and its utility as having anti-cancer activity in docetaxel-resistant mCRPC and breast cancer patients. For the same reasons, we give little weight to Patent Owner's criticisms of Dr. Seth's testimony in support of Petitioner's Reply, which are effectively rebutted by Petitioner. *See* Paper 80 (Observations on the Cross-Examination of Dr. Seth); Paper 93 (Response to Observations on the Cross-Examination of Dr. Seth).

Patent Owner further contends it is contradictory for Petitioner to argue that cabazitaxel's similarities with docetaxel disposed it to have activity against prostate cancer and breast cancer but that its differences allowed it to overcome at least some mechanisms of docetaxel resistance. PO Resp. 21–23, 29–33. Patent Owner emphasizes other tubulin-binding compounds, such as larotaxel that "failed in three separate phase III studies." *Id.* at 22–23; *see also id.* at 29–33 (discussing failure of phase III studies and failure to achieve FDA regulatory approval). We reiterate, achievement of successful phase III study results for FDA approval is not the appropriate standard for measuring success. We also credit Petitioner's evidence that cabazitaxel was designed to retain the tubulin-binding activity known to make docetaxel lethal to cancer cells while simultaneously reducing its affinity for the so-called P-gp pump (P-glycoprotein pump). Pet. 8 (citing Ex. 1010, 1547–48), 22–23 (citing Ex. 1002 ¶¶ 66–69); Reply 8 (citing Ex. 1002 ¶¶ 60, 66–69, 77; Ex. 1021, 75). Such information would have been known to a POSA – a clinical oncologist with experience treating metastatic prostate cancer and access to information regarding pharmacokinetics and mechanisms of drug resistance – as a major mechanism of docetaxel resistance. As explained by Dr. Seth, a POSA would have believed cabazitaxel was (like docetaxel) active against both breast and prostate cancer. Ex. 1043 ¶ 25; *see also* Ex. 1050, 354. Moreover, preclinical and clinical studies confirmed that cabazitaxel was active against docetaxel-resistant prostate and breast cancer. Ex. 1010, 1550 (Col. 2 ¶ 3)–1551 (Col. 1 ¶ 1, Table 3); Ex. 1022, 163 (Col. 2 ¶¶ 4–5).

Patent Owner's remaining arguments are similarly unavailing because, as explained above, Patent Owner applies an inappropriate measure of success in its analysis. *See e.g.*, PO Resp. 28 (positive patient response in phase I study insufficient to prove "cabazitaxel would successfully treat prostate cancer"), 31 ("phase II studies in oncology are poorly predictive of phase III success"), 38 ("Dr. Seth admitted a POSA could not predict beforehand whether a phase III trial was going to be successful or a failure."), 39 (regarding Winquist and the TROPIC Listing, "mere existence of a phase III study was not indicative of success"), 42 ("none of the references cited by Mylan disclose any data on the ability of cabazitaxel to increase the overall survival of any patients").

For the reasons given above, we determine Petitioner has shown by a preponderance of the evidence that a POSA, based on Winquist and the TROPIC Listing in view of Attard, Beardsley, and the knowledge of a POSA, would have had a reasonable expectation of success in achieving the method of treatment recited in claims 1 and 27 of the '592 patent.

d. Secondary Considerations

Secondary considerations, when present, must "be considered en route to a determination of obviousness." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (citation omitted). Secondary considerations may include any of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *See Graham*, 383 U.S. at 17; *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). Patent Owner bears the burden of producing objective evidence of nonobviousness in rebuttal to Petitioner's evidence of obviousness. *Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1101–02 (Fed. Cir. 2015).

For objective evidence of nonobviousness to carry substantial weight, "its proponent must establish a nexus between the evidence and the merits of the *claimed invention*." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (citing *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)); *see also In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). A patent owner may establish a rebuttable presumption of nexus "when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'" *WBIP LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016). We note some tension in applicable Federal Circuit precedent regarding the standard for establishing an appropriate nexus. On the one hand, "[w]here the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention," i.e., "there must be a nexus to some aspect of the claim not already in the prior art." *Kao*, 639 F.3d at 1068–69. On the other hand, there is no requirement that "objective evidence must be tied exclusively to claim elements that are not disclosed in a particular prior art reference in order for that evidence to carry substantial weight." *WBIP*, 829 F.3d at 1331. A patent owner may show, for example, "that it is the claimed combination as a whole that serves as a nexus for the objective evidence;

proof of nexus is not limited to only when objective evidence is tied to the supposedly 'new' feature(s)." *Id.* Ultimately, the fact finder must weigh the secondary considerations evidence presented in the context of whether the claimed invention as a whole would have been obvious to a POSA. *Id.* at 1331–32.

Patent Owner presents argument and evidence of long-felt need, failure of others, unexpected properties, praise, commercial success, and copying. PO Resp. 50–56. Patent Owner's objective evidence of non-obviousness is tied to the commercial success and recognition of Jevtana®, the successful phase III clinical trial results from the TROPIC Study that led to expedited FDA review and approval of Jevtana®, and the assertion that it was unexpected for cabazitaxel therapy to provide a statistically significant survival benefit and reduced side effects in docetaxel-refractory mCRPC patients. PO Resp. 50–56 (citing Ex. 2176 ¶¶ 93, 185, 187–189, 192–195, 198, 200–202, 204–207, 209–214, 216–219, 221). Patent Owner also produces evidence that clinical administration of Jevtana® according to its FDA-approved labeling satisfies the limitations of independent claims 1 and 27, as well as several dependent claims, of the '592 patent. PO Resp. 54 n.2 (citing Ex. 2150, 1; Ex. 2176 ¶¶ 192–195).

Petitioner offers rebuttal evidence contesting Patent Owner's secondary considerations evidence and the asserted nexus to the claimed treatment method. Reply 17–23.

We have considered Petitioner's evidence of the obviousness of claims 1 and 27, set forth above, in conjunction with Patent Owner's objective evidence of non-obviousness and Petitioner's rebuttal evidence.

On balance, we conclude that Patent Owner's secondary considerations evidence does not outweigh Petitioner's strong evidence of obviousness.

(i) Presumption of nexus

We begin with the observation that the clinical administration of Jevtana® is an embodiment of the claimed treatment method. Ex. 2176 ¶¶ 192–195. Petitioner does not directly contest this testimony, but raises related arguments that we address below. Reply 4–5, 17–18. Therefore, we credit Dr. Sartor's cited Declaration testimony and begin by presuming a nexus between alleged long-felt need, failure of others, unexpected results, praise, commercial success, and copying and the administration of Jevtana® to docetaxel-refractory mCRPC patients. The presumption shifts the burden of producing rebuttal evidence to Petitioner. *WBIP*, 829 F.3d at 1329.

The Board, a non-jury tribunal with administrative expertise, is well-positioned to determine and assign appropriate weight to the evidence presented. *See Gnosis S.p.A. v. S. Alabama Med. Sci. Found.*, Case IPR2013-00118, slip op. at 43 (PTAB June 20, 2014) (Paper 64); *see also Donnelly Garment Co. v. NLRB*, 123 F.2d 215, 224 (8th Cir. 1941) ("One who is capable of ruling accurately upon the admissibility of evidence is equally capable of sifting it accurately after it has been received."). In rendering our decision, we have assigned weight to the evidence as appropriate in view of the entire record before us. For the reasons that follow, we determine Petitioner's evidence effectively rebuts the presumption of nexus and the weight to be given Patent Owner's objective evidence of non-obviousness.

(ii) Claimed method disclosed in the prior art

The claimed treatment method is fully disclosed in the prior art. Pet. 7–9 (citing Ex. 1008; Ex. 1009, 3948; Ex. 1010, 1547–49, 1551; Ex. 1012, 724, 729); Reply 4–5 (citing, *inter alia*, Ex. 1041, 59:7–20, 62:8–18, 65:2–18, 67:23–68:6, 71:16–25; 73:10–15; 83:10–15, 87:13–88:4, 93:9–17, 96:17–22, 97:7–100:4; 150:6–152:6). The same treatment method described in the ’592 patent, specifically the administration of a 25 mg/m^2 dose of cabazitaxel in combination with prednisone to docetaxel-refractory mCRPC patients, as set out in the TROPIC Study, was disclosed in the prior art Winquist and TROPIC Listing references. This is not a case where isolated claim limitations are disclosed individually in different prior art references and the claimed combination itself provides the nexus to the merits of the invention. *See WBIP*, 829 F.3d at 1330; *see also* Reply 5 (citing, *inter alia*, *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1353–1354 (Fed. Cir. 2012) (method of treating gastric acid disorder by administering an obvious formulation “cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations”)).

First, a POSA would have read Winquist and the TROPIC Listing together because they disclose the same clinical study. Winquist and the TROPIC Listing disclose the same treatment method being used in the same clinical trial for treating the same patient population – the Sanofi-Aventis TROPIC Study. Ex. 1002 ¶¶ 118–120; *see also* Ex. 1041, 94:14–95:4 (“I would anticipate that if they [a POSA] had the available information, they would read both.”). Second, a POSA would have understood Winquist, which discloses administering a 25 mg/m^2 dose of cabazitaxel in combination with prednisone to mCRPC patients “previously treated with a

Taxotere [docetaxel]-containing regimen" (Ex. 1009, 3948), as disclosing the treatment of prostate cancer that "has progressed during or after treatment with docetaxel," as recited in claims 1 and 27. Ex. 1002 ¶¶ 65, 117 ("It is implicit in treatment of a patient with mCRPC who has been previously . . . treated with docetaxel that such treatment is necessary because progression occurred during or after docetaxel treatment."). Dr. Sartor also testifies that a patient previously treated with docetaxel, as stated in Winquist, would not have been treated with a follow-on taxane such as cabazitaxel "until there's evidence of progression." Reply 4 (citing Ex. 1041, 59:7-20, *see also id.* at 93:9–17 ("If the patient had not progressed, then he likely would not be treated with cabazitaxel."). Thus, the method steps recited in claims 1 and 27 are not disclosed in isolation in the prior art; they are disclosed in the same combination claimed and exemplified in the '592 patent.

In short, Petitioner's evidence effectively rebuts the legal presumption of a nexus between the administration of Jevtana® to treat mCRPC patients and "some aspect of the claim not already in the prior art." *Kao*, 639 F.3d at 1068–69.

(iii) Commercial success

Patent Owner relies on a presumed nexus between the '592 patent claims and the commercial success of Jevtana®. PO Resp. 55–56. Petitioner responds that Patent Owner has listed "at least eight different patents" in the FDA Orange Book for Jevtana®, of which six have expired, and that Patent Owner fails to explain why Jevtana®'s commercial success is attributable to the treatment method of the '592 patent rather than to prior art elements of the expired patents. Reply 17–18 (citing Ex. 1044 ¶¶ 17–22, 124–30). We reproduce Mr. McSorely's chart of Orange Book-listed patents, below.

Figure A

Other Jevtana® Orange Book Listed Patents

U.S. Patent No.	Filing Date	Issue Date	Expiration Date	Assignee
5,438,072	11/22/93	8/1/95	11/22/13	Rhone-Poulenc Rorer S.A.
5,698,582	3/3/95	12/16/97	7/3/12	Rhone-Poulenc Rorer S.A.
5,847,170	3/26/96	12/8/98	3/26/16	Rhone-Poulenc Rorer S.A.
6,331,635	4/28/98	12/18/01	3/26/13	Aventis Pharma S.A.
6,372,780	1/3/01	4/16/02	3/26/13	Aventis Pharma S.A.
6,387,946	9/25/01	5/14/02	3/26/13	Aventis Pharma S.A.
7,241,907	9/17/04	7/10/07	12/10/25	Aventis Pharma S.A.
8,927,592	4/26/12	1/6/15	10/27/30	Aventis Pharma S.A.

Ex. 1044 ¶ 19, Attachment 4.1. As shown in the Orange Book patent chart, above, Patent Owner has listed seven earlier-issued patents covering Jevtana®, six of which have now expired and one of which does not expire until December 10, 2025. *Id.*; *see also* Ex. 1059, 1027. The first three listed patents, for example, disclose taxane compounds and compositions. Ex. 180; Ex. 1081; Ex. 1082.

We agree with Petitioner that the presumed nexus between Jevtana®'s commercial success and the '592 patent claims is undercut by the Patent Owner's failure to acknowledge or address the seven prior art Orange Book-listed patents for Jevtana®. Mr. Tate affirmatively states in his declaration, and confirms in his deposition testimony, that he was not asked to provide any opinion on a nexus between the commercial success of Jevtana® and the claims of the '592 patent. Ex. 2149 ¶ 25 n.49; Ex. 1042, 64:19–65:20, 78:14–8. He testifies that he relied on Dr. Sartor to establish such a nexus. Ex. 1042, 65:21–66:8; *see also* Ex. 2149 ¶¶ 25–27, Schedule 3.

Dr. Sartor provides only a conclusory statement: "In my opinion, Jevtana®'s success is attributable to the inventions claimed in the '592 patent, which reflect the results of the TROPIC study that led to FDA approval." Ex. 2176 ¶ 219; *see also id.* ¶¶ 221–222. Dr. Sartor does not discuss any of the other Orange Book patents for Jevtana®, whether Jevtana®'s commercial success may be tied to the inventions of those patents, such as the composition patents, or why Jevtana®'s commercial success should be attributable solely to the claimed treatment method of the '592 patent. Dr. Sartor, moreover, testifies that he understood the invention of the '592 patent to be cabazitaxel and its utility. Ex. 1041, 143:25–144:23. Dr. Sartor further testifies that, in his opinion, the 25 mg/m^2 dose of cabazitaxel "is critical," but he readily acknowledges that the critical dose was disclosed in the prior art Winquist reference. *Id.* at 150:25–151:17. Dr. Sartor also admitted that, although the critical dose was disclosed in Winquist, he "didn't view this as part of the prior art." *Id.* at 151:18–152:6. As with Patent Owner's no-reasonable-expectation-of success argument, such inconsistency undermines Patent Owner's commercial success argument.

"Where market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013); *see also Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) ("[f]inancial success is not significantly probative of [whether the claimed invention was non-obvious in light of prior art] in this case because others were legally barred from commercially testing the [relevant] ideas" by other patents covering the product). Six of the Jevtana® Orange Book patents have now expired, and, as in *Galderma* and *Merck*, market access by others previously was precluded. Ex. 1059, 1027 ("EXCLUSIVITY EXPIRATION DATE JUN 17, 2015"). Therefore, for this additional reason, any inference of non-obviousness from Jevtana®'s commercial success is weak.

In sum, we are persuaded that Petitioner's evidence and argument effectively rebuts the presumption of nexus between the commercial success of Jevtana® and the claimed treatment method of the '592 patent.

(iv) Long-felt need

Patent Owner argues that there was a need to treat critically ill mCRPC patients whose disease had progressed after docetaxel therapy, and that cabazitaxel "was the first therapy to show a survival benefit with patients that progressed after docetaxel." PO Resp. 50 (citing Ex. 2071, 1; Ex. 2176 ¶¶ 198, 200–202; Ex. 2177, 43:11–17). Patent Owner emphasizes that, based on the successful phase III clinical trial data from the TROPIC Study, the FDA accelerated approval of Jevtana® in only 11 weeks. *Id.* at 50–51 (citing Ex. 2059, 1 (¶ 3); Ex. 2068, 1). Patent Owner provides objective evidence that the accelerated approval of Jevtana® "fill[ed] a critical gap among patients with the most advanced stage of prostate cancer and is the first therapeutic option for these patients shown to prolong survival." *Id.* (citing Ex. 2068, 1).

Petitioner challenges Patent Owner's evidence by trying to shift the focus onto later-approved drugs that have since overtaken Jevtana® in treating mCRPC patients and in terms of sales. Reply 18–19 (citing Ex. 1041, 187:21–189:14, 191:8–193:12, 194:12–195:9, 196:6–23, 197:6–199:5, 200:15–201:18, 204:5–205:6, 222:6–16, 225:17–21; Ex. 1043 ¶ 34; Ex. 1044 ¶¶ 34–51; Ex. 1069). Petitioner also derides the alleged need as "'kicking the can down the road.'" *Id.* at 18 (citing Ex. 1041, 200:9–21). We are not persuaded by Petitioner's rebuttal evidence regarding long-felt need.

Patent Owner's evidence, on this record, demonstrates the importance of the phase III clinical trial results in motivating FDA fast-track approval for Jevtana®. At the time of its approval, Jevtana® was the first FDA-approved therapy for treating docetaxel-refractory mCRPC patients. PO Resp. 50–51 (citing Ex. 2059, 1; Ex. 2068, 1; Ex. 2071, 1; Ex. 2176 ¶¶ 200–202; Ex. 2177, 43:11–17). The fact that later-approved drugs may have been an improvement over Jevtana® in the treatment of such critically ill patients is beside the point. We do, however, reiterate that the weight we give to Patent Owner's evidence of long-felt need is tempered by Petitioner's evidence that the TROPIC Study treatment protocol, the results of which provided the impetus for FDA fast-track approval, was disclosed in the prior art along with evidence of anti-cancer activity in docetaxel-refractory mCRPC and metastatic breast cancer patients. Ex. 1008; Ex. 1009, 3948; Ex. 1010; Ex. 1012, 723, 727. In addition, and as discussed above, Petitioner has provided persuasive evidence to rebut the presumed nexus between the '592 patent's claimed treatment method and the success of Jevtana®.

(v) Failure of others

Our analysis of long-felt need applies equally to Patent Owner's evidence of the failure of others to increase survival of docetaxel-refractory mCRPC patients prior to the approval of Jevtana®. PO Resp. 51 (citing, *inter alia*, Ex. 1022, 162–63; Ex. 2008, 1; Ex. 2026, 77–79; Ex. 2041, 808; Ex. 2096, 2973 (Col. 2 ¶ 2) (discussing two decades of efforts to overcome taxane resistance); Ex. 2176 ¶¶ 204–207). Petitioner's response is essentially the same as the response it proffered in rebuttal to Patent Owner's long-felt need evidence, with like effect. Reply 19.

(vi) Unexpected results

Patent Owner argues it was unexpected that cabazitaxel therapy would "prolong overall survival" in docetaxel-refractory mCRPC patients, with reduced side effects, as shown in the TROPIC Study. PO Resp. 52–54 (citing Ex. 2176 ¶¶ 39, 93, 185, 187–89, 209–214; Ex. 2177, 43:11–17, 45:16–46:2). In addition to a long-felt need and the failure of others, referenced immediately above, Patent Owner emphasizes that the positive results of the TROPIC Study were particularly unexpected in light of the lack of a phase II study in prostate cancer and the fact that the disease had progressed in patients after receiving a taxane (docetaxel) therapy. *Id.* at 52 (citing Ex. 2176 ¶¶ 185, 188–89, 210). With regard to side effects, Patent Owner sets up a logical tautology from its characterization of Petitioner's argument that, if a POSA would have expected cabazitaxel to act similarly to docetaxel, then a POSA would not have expected cabazitaxel therapy to have a "lower incidence of side effects such as neuropathy, alopecia [hair loss], nail changes and dysgeusia [altered taste sensation] than docetaxel." *Id.* at 54 (citing Ex. 2176 ¶¶ 211–214).

Petitioner responds with Dr. Sartor's acknowledgment that critical features of the claimed invention, particularly the 25 mg/m^2 dose of cabazitaxel and the docetaxel-refractory patient population, were disclosed in the prior art Winquist (Ex. 1009) and TROPIC Listing (Ex. 1008) references. Reply 20 (citing Ex. 1041, 150:25–151:17, 152:22–153:10). Therefore, Petitioner argues, there is no basis to attribute any prolonged survival to a claimed feature not already disclosed in the prior art. *Id.*

We view the evidence of unexpected results as neutral in this case. On the one hand, the results of the TROPIC Study were unexpected enough to result in FDA fast-track approval of the first therapy for docetaxel-refractory mCRPC patients. On the other hand, a statistically significant increase in overall survival of a patient population is not a claim limitation of the '592 patent claims. The claimed method also was disclosed in the prior art (Winquist and TROPIC Listing), and Attard (Ex. 1021, 74–75) and Beardsley (Ex. 1022, 163) note the positive anticancer activity and partial responses to cabazitaxel therapy in docetaxel-refractory phase I (mCRPC) and phase II (metastatic breast cancer) patients. Beardsley expressly notes that the results in docetaxel-refractory patients were sufficient to permit moving directly to the phase III TROPIC Study, which compared cabazitaxel plus prednisone therapy to palliative mitoxantrone plus prednisone therapy in docetaxel-refractory mCRPC patients.[16] Ex. 1022,

[16] We give no weight to Petitioner's unsupported argument that Patent Owner failed to compare cabazitaxel therapy survival rates to docetaxel re-challenge survival rates. Reply 20. As Dr. Sartor explains, mitoxantrone plus prednisone therapy was the *de facto* standard of care for docetaxel-refractory patients at the time of the earliest possible priority date of the '592 patent. Ex. 1027, 557; Ex. 2176 ¶ 39.

163 (Col. 2 ¶ 5). Beardsley's explanation effectively undermines Patent Owner's argument that the TROPIC Study results were particularly unexpected given the absence of a phase II clinical trial in mCRPC patients.

As stated previously, Petitioner's evidence is sufficient to establish that a POSA would have had a reasonable expectation that the TROPIC Study protocol disclosed in Winquist and the TROPIC Listing would result in anticancer activity. Winquist and the TROPIC Listing also note that prolonging patient survival ("overall survival") was the primary endpoint of the study, which had been ongoing since 2006. Ex. 1008, 2; Ex. 1002 ¶ 122. Patent Owner's additional evidence, regarding alleged reduced side effects resulting from cabazitaxel therapy in comparison to docetaxel therapy, does not alter our view of the unexpected results evidence. We credit Dr. Seth's testimony that Pivot disclosed a "favorable" safety profile for cabazitaxel therapy in comparison to docetaxel, including side effects such as nausea, vomiting, and sensory neuropathy. Ex. 1043 ¶ 31; Ex. 1010, 1551.

Therefore, on balance, we determine the unexpected results evidence does not support Patent Owner's nonobviousness argument in this case.

(vii) Praise for Jevtana®

Patent Owner again relies on the evidence of FDA fast-track approval in support of its argument that Jevtana® received praise. PO Resp. 54 (citing Ex. 2059, 1). Patent Owner provides evidence of post-approval articles and press releases praising Jevtana® as a "major success in second line chemotherapy for advance[d] prostate cancer," based on its increase in overall patient survival in the TROPIC Study. *Id.* (citing Ex. 2071, 1 (Col. 1), 3). Others praised Jevtana® for giving patients more time to live and allowing them to "carry on doing the things they enjoy despite their cancer." *Id.* at 55 (citing Ex. 2115, 2).

Petitioner responds that the news article cited by Patent Owner, Exhibit 2115, also states that the "Cancer Drugs Fund plans to axe drug [Jevtana] from its approved list" because "it is not cost-effective and doesn't offer 'sufficient clinical benefit.'" Reply 21 (citing Ex. 2115, 1–2). Petitioner again argues absence of a nexus to a novel feature of the '592 patent claims, and it also argues the "buzz" surrounding Jevtana®'s approval was not as significant as the "big buzz" received by later drugs approved to treat the same patient population. *Id.* (citing Ex. 1041, 201:19–202:14).

Patent Owner's evidence establishes a modicum of industry praise for Jevtana® upon FDA approval and thereafter. However, as with our analysis of long-felt need, failure of others, and unexpected results, the weight we give to Patent Owner's evidence of praise is tempered by Petitioner's evidence that the TROPIC Study treatment protocol, the results of which provided the impetus for FDA fast-track approval, was disclosed in the prior art along with evidence of anti-cancer activity in docetaxel-refractory mCRPC and metastatic breast cancer patients. Ex. 1008; Ex. 1009, 3948; Ex. 1010; Ex. 1012, 723, 727. In addition, and as discussed above, Petitioner has provided persuasive evidence to rebut the presumed nexus between the '592 patent's claimed treatment method and the success of Jevtana®.

(viii) Copying

Patent Owner provides only a cursory, conclusory assertion that nine competitors are accused of infringing the '592 patent claims in district court litigation to support its copying argument. PO Resp. 56 (citing Paper 6, 2–3;

Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 759 (N.D. W.Va. 2004) (generic manufacturer's decision to copy a drug is probative of nonobviousness)). Patent Owner does not offer any direct evidence of alleged copying. *Id.* Therefore, Patent Owner's conclusory argument does not support an inference of non-obviousness.

e. Conclusion

When we balance Petitioner's strong evidence of obviousness against the objective evidence of nonobviousness, we determine that a preponderance of the evidence supports Petitioner's position that claims 1 and 27 of the '592 patent are unpatentable for obviousness over Winquist and the TROPIC Listing, in view of Attard and Beardsley.

5. Dependent Claims 2, 5, 12, 15–26, and 28–30

Petitioner argues that dependent claims 2, 5, 12, 15–26, and 28–30 recite additional limitations that would have been obvious to a POSA based on Winquist, the TROPIC Listing, and Pivot.[17] Pet. 29–32, 34–38, 43–45. Petitioner supports its arguments with claim charts for most of the claims, which contain citations to Winquist, the TROPIC Listing, and Dr. Seth's Declaration. *Id.* at 35–38 (citing Ex. 1008; Ex. 1009; Ex. 1002). Having reviewed the complete trial record, we are persuaded Petitioner has proved by a preponderance of the evidence that Winquist, the TROPIC Listing, and

[17] We note dependent claims 15–16, 21, 26, and 30 referenced in this section were raised in other instituted grounds. Paper 9, 21–23. Because Patent Owner addresses the cabazitaxel dosage limitations recited in those dependent claims together with the cabazitaxel dosage limitations recited in claims 12, 18, 22, 24, and 28 (PO Resp. 44–45), for convenience we address the claims reciting cabazitaxel dosage limitations together in this section.

Pivot disclose the elements recited in dependent claims 2, 5, 12, 15–26, and 28–30. Pet. 29–32, 34–38, 42–45; Ex. 1002 ¶¶ 49–50, 61–62, 123, 126–130, 136–137, 139, 154, 157–160.

For example, Winquist and the TROPIC Listing disclose administration of cabazitaxel in combination with a corticoid to castration-resistant, metastatic prostate cancer patients (claims 2, 20, and 24). Ex. 1008, 1–2; Ex. 1009, 3948; Ex. 1002 ¶¶ 123, 127–130. Winquist and the TROPIC Listing also disclose repeating the administration of cabazitaxel as a new cycle every three weeks (claims 5, 19, 23, 25, and 29). Ex. 1008, 1; Ex. 1009, 3948; Ex. 1002 ¶ 137. They further disclose administering cabazitaxel in combination with prednisone (claims 24 and 27). Ex. 1008, 1; Ex. 1009, 3948; Ex. 1002 ¶¶ 126, 129, 135. To the extent not stated expressly above, we adopt Petitioner's arguments and evidence in support of our findings that Winquist, the TROPIC Listing, and Pivot disclose the limitations recited in claims 2, 5, 12, 15–26, and 28–30 of the '592 patent. Pet. 25–38, 43–45. Motivation to combine and reasonable expectation of success are addressed in Section II.B.4, above, and further in response to Patent Owner's arguments, below.

Patent Owner challenges Petitioner's proofs regarding whether a POSA would have had a reasonable expectation of success in administering the cabazitaxel doses recited in claims 12, 15–16, 18, 21–22, 24, 26, 28, and 30. PO Resp. 44–45. Claims 12, 16, 18, 22, 24, and 28 recite administration of a 25 mg/m^2 dose of cabazitaxel, and claims 15, 21, 26, and 30 recite a 20 mg/m^2 cabazitaxel dose. Petitioner argues that Winquist discloses administration of the 25 mg/m^2 dose, and Pivot discloses administration of the 20 mg/m^2 dose that was well tolerated in docetaxel-refractory metastatic breast cancer patients. Pet. 36–38 (citing Ex. 1009, 3948; Ex. 1002 ¶ 139), 43–46 (citing Ex. 1002 ¶¶ 157–158, 160; Ex. 1010, 1547–48, 1550).

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 (Col. 2 ¶ 3). Pivot explains that the 20 mg/m^2 dose was the "recommended dose for phase II and III studies" based on earlier phase I studies. *Id.* at 1548 (Col. 1 ¶ 2); *see also* Ex. 1002 ¶ 157 ("Pivot . . . provides reasons for this dose."). Pivot further discloses that cabazitaxel was initially administered at a 20 mg/m^2 dose, and thereafter "escalation up to 25 mg/m^2 from cycle 2, in selected patients, on the basis of their good tolerance in cycle 1, was feasible in 20 patients (28%) with no evident increase in the overall incidence of subsequent AEs [adverse events] in this group." Ex. 1010, 1550 (Col. 1 ¶ 2). Based on the study data, in which 72% of taxane-refractory metastatic breast cancer patients were treated at a dose of 20 mg/m^2 and 28% of patients at a 25 mg/m^2 dose, Pivot concluded that cabazitaxel "was active and well tolerated in . . . patients with taxane-resistant disease." *Id.* at 1547 ("Conclusions"); *see also id.* at 1548–49. Therefore, Pivot discloses the active and well-tolerated use of both 20 and 25 mg/m^2 doses of cabazitaxel in docetaxel-refractory metastatic breast cancer patients.

Patent Owner argues that a POSA would not have expected any clinical benefit to outweigh known toxic side effects from administering cabazitaxel at a dose of 25 mg/m^2 or even at the lower 20 mg/m^2 dose. PO Resp. 44–45 (citing Ex. 2176 ¶¶ 172–174; Ex. 2177, 72:17–73:2, 73:14–23, 130:14–131:2; Ex. 2229, 2). Patent Owner particularly emphasizes the risk of life-threatening neutropenia in the absence of clinical trial data, arguing it would have been "unreasonable for a POSA to expect that this dose of cabazitaxel [20 mg/m^2] would prolong overall survival prior to the results of TROPIC described in the '592 patent." *Id.* at 44. For the reasons given in Section II.B.4, above, Patent Owner uses the incorrect standard for measuring a reasonable expectation of success in achieving the claimed invention. We further note the '592 patent does not describe any clinical trial results for a 20 mg/m^2 dose of cabazitaxel, even though dependent claims 15, 21, 26, and 30 recite a 20 mg/m^2 dose. This fact tends to undercut Patent Owner's argument that clinical trial results are necessary to support a reasonable expectation of success.

We also are not persuaded by Patent Owner's argument of no reasonable expectation of success in view of potentially toxic side effects, particularly because Winquist and Pivot disclose the administration of the recited cabazitaxel doses, and Pivot describes how an experienced oncologist would manage the emergence of side effects with dose control, antihistamines, and antiemetics. Ex. 1010, 1548 (Col. 2 ¶ 3). Pivot expressly discloses that the recommended dose of 20 mg/m^2 cabazitaxel was well tolerated in most patients and that a substantial number of patients were escalated up to a 25 mg/m^2 dose without dose-limiting adverse events such as severe neutropenia. *Id.*; *see also id.* at 1547 ("XRP6258 [cabazitaxel] was active and well tolerated in this group of MBC patients with taxane-resistant disease."), 1551 ("The safety profile of XRP6258 was very favorable when compared with the known safety profile of the marketed taxanes or other compounds under development."). The potential for severe side effects in such desperately ill patients was not enough to prevent Patent Owner from selecting the higher 25 mg/m^2 cabazitaxel dose for administration in the large phase III TROPIC Study disclosed in Winquist. Ex. 1009.

We credit Dr. Seth's testimony that "Pivot's two doses (20 and 25 mg/m^2) were in agreement with the Phase I data regarding safe doses reported in Mita, as well as the Phase III doses reported in Winquist and the TROPIC Listing." Ex. 1043 ¶ 30. Moreover, Dr. Sartor testifies that when he treats mCRPC patients, even today, he prescribes drugs that are not approved by the FDA for such a treatment indication, which means there are no phase III clinical trial results available. Ex. 1041, 180:22–182:15, 183:23–184:4, 185:8–22. He testifies that he treats a small percentage of patients with "non-FDA-approved therapies" when "they're not in a clinical trial," that he does so without the benefit of any phase III clinical data, and that he thinks "that's probably typical of other oncologists" as well. *Id.* at 182:16–183:10, 183:23–185:7. Dr. Sartor's candid acknowledgement that treatment of advanced prostate cancer patients with off-label drugs is a type of "desperation oncology," further undercuts Patent Owner's argument that side effects and lack of phase III clinical trial data would have made it unreasonable for a POSA to administer a 20 mg/m^2 or 25 mg/m^2 dose of cabazitaxel to treat docetaxel-refractory mCRPC patients.

Based on the complete trial record, we determine Petitioner has proved by a preponderance of the evidence that dependent claims 2, 5, 12, 15–26, and 28–30 of the '592 patent are unpatentable as obvious under 35 U.S.C. § 103.

C. Ground 2: Asserted Obviousness of Claims 3 and 4 over Winquist, the TROPIC Listing, and Didier

Claim 3 depends from claim 1 and recites cabazitaxel "in the form of an acetone solvate." Ex. 1001, 18:61–62. Claim 4 depends from claim 3 and further recites "the acetone solvate contains between 5% and 8% by weight of acetone." *Id.* at 18:63–64. The '592 patent describes a solvate as "a molecular complex characterized by the incorporation of the crystallization solvent [acetone] into the crystal of the molecule of the active principle." Ex. 1001, 4:40–47. The acetone solvate form of cabazitaxel is used to prepare a premix for subsequent dilution in an aqueous perfusion solution at the time of intravenous administration. *Id.* at 5:12–29.

Petitioner acknowledges that Winquist and the TROPIC Listing do not disclose an acetone solvate form of cabazitaxel. Pet. 38. Petitioner, however, relies on Didier's teaching of the preparation of an acetone solvate form of cabazitaxel where the "mean value of the content of acetone is 7%." *Id.* at 38–39 (citing Ex. 1011, 2:39–42). Claim 2 of Didier teaches an acetone solvate form of cabazitaxel "comprising from about 5 to about 7 percent by weight of acetone." Ex. 1011, 4:1–5. Didier also states that cabazitaxel "exhibits noteworthy anticancer and antileukemic properties," which suggests the potential use of an acetone solvate form of the drug for cancer treatment. Ex. 1011, 1:22–23; Ex. 1002 ¶ 141.

Petitioner, relying on Dr. Seth's testimony, argues that a POSA would have known that non-aqueous solvates, such as acetone, could improve the water solubility of highly lipophilic taxanes. Pet. 39 (citing Ex. 1002 ¶¶ 80–81 (discussing Liu[18])). Given that the TROPIC Listing discloses cabazitaxel administration by intravenous infusion (Ex. 1008, 2), Petitioner argues a POSA would have had strong reasons to prepare cabazitaxel in a solvate

[18] Liu, *Water-Insoluble Drug Formulation*, Chapter 15, 525–68 (CRC Press 2000) ("Liu"). Ex. 1025.

form to "enable the drug's dissolution into an aqueous solution suitable for intravenous infusion into a patient." Pet. 39 (citing Ex. 1002 ¶ 142). Petitioner argues that Didier would have motivated a POSA to select acetone as the solvate of choice for cabazitaxel, at a 7% acetone weight ratio and with a reasonable expectation of success, because Didier expressly discloses and validates this particular crystalline form of cabazitaxel. *Id.* at 39–40 (citing Ex. 1002 ¶ 142; Ex. 1011, 2:39–42, 4:1–5).

Patent Owner challenges Petitioner's evidence, particularly Liu, as failing to support a motivation for a POSA to select Didier's acetone solvate form of cabazitaxel for use in the intravenous treatment method disclosed in the TROPIC Listing. PO Resp. 47–49. Patent Owner argues that Liu does not support Dr. Seth's opinion because, when a highly lipophilic drug such as cabazitaxel presents a solubility problem, Liu suggests the use of other techniques including co-solvents, pro-drugs, emulsions, surfactants, and liposomes rather than alteration of the solid state form of the drug compound (e.g., forming a solvate) to achieve the requisite solubility. *Id.* at 47–48 (citing Ex. 1025, 526–27; Ex. 2069). Patent Owner further argues that Liu's list of solvents, including acetone, are not suitable for pharmaceutical preparations due to "potential toxicity" and do not support Petitioner's asserted motivation to combine. *Id.* at 48 (citing Ex. 1025, 529, 531; Ex. 2057, 67381, 67383).

We are persuaded by a preponderance of the evidence that a POSA would have been motivated by the teachings of Didier, with a reasonable expectation of success, to use an acetone solvate form of cabazitaxel at a weight ratio of approximately 7% to solubilize cabazitaxel for intravenous administration. Although Patent Owner emphasizes the general teaching of

Liu that alternate solubility techniques were available to solubilize lipophilic molecules, Patent Owner does not effectively rebut the fact that the claimed acetone solvate form of cabazitaxel, and a method for preparing it, is expressly disclosed in Didier. Moreover, as to Liu, a reference does not teach away if it expresses a general preference for an alternative approach from among known options available to a POSA, particularly if the reference does not "criticize, discredit, or otherwise discourage the solution claimed." *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Liu's statement that alteration of a molecule's solid state "may have little effect on its solubility" is not a criticism, disparagement, or other teaching away from the use of an acetone solvate form of cabazitaxel. Liu goes on to note that disrupting the crystal lattice structure to increase solubility "can be done by altering the crystal form (polymorphs or solvates/hydrates)." Ex. 1025, 527–28. Such a teaching is entirely consistent with the teachings of Didier and the knowledge of a POSA that formation of an acetone solvate was a known option, among others, for improving solubility of lipophilic molecules.

We acknowledge Patent Owner's evidence regarding "potential toxicity" of solvents such as acetone used to formulate a drug product (Ex. 1025; Ex. 2057), but the cited FDA guidance considers acetone to be a Class 3 solvent that "may be regarded as less toxic and of lower risk to human health" than Class 1 or Class 2 solvents, which are to be avoided altogether or very strictly limited. Ex. 2057, 67380–81. The FDA guidance states that "Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals." *Id.* at 67381. In short, low levels of acetone – "50 mg per day or less" – in a pharmaceutical product "would be acceptable without justification." *Id.* The FDA Guidance provides meaningful context for Liu's general comment regarding the "potential toxicity" of "other solvates" apart from hydrates and anhydrous solid state forms. Ex. 1025, 531. Patent Owner does not provide evidence to suggest that the levels of acetone in Didier's acetone solvate form of cabazitaxel (a 5% to 7 % weight ratio, Ex. 1011, 4:1–5) would run afoul of the FDA Guidance for acceptable acetone levels if administered intravenously at a 25 mg/m^2 dose as disclosed in Winquist and the TROPIC Listing.

We also credit Dr. Seth's testimony that "it was well known in the art as of October 29, 2009 that non-aqueous solvates, including acetone solvates, could be used to make soluble forms of taxanes suitable for intravenous delivery." Ex. 1002 ¶ 80; Ex. 2177, 176:6–177:2. Although hydrates and anhydrous forms of taxanes also were known (PO Resp. 48–49), we are persuaded by Dr. Seth's testimony that any question regarding potential toxicity from the use of acetone solvates did not amount to a teaching away from their use in favor of hydrates and anhydrous crystalline forms. Ex. 2177, 177:4–19 ("a POSA in 2009, acetone most likely would be the most readily available usage."), 179:23–180:7 ("[I]n 2009 we were -- I had used acetone in my fellowship at Stony Brook"), 180:26–181:10 ("[I]n 2009 that's a fair statement to say that a POSA could choose probably ethanol versus acetone. It would be a 50/50 choice."). Dr. Seth's testimony also persuades us, on balance, that the use of an acetone solvate form of cabazitaxel for intravenous delivery, as disclosed in Winquist and the TROPIC Listing, would not have presented a toxicity problem of such magnitude that it would tip the evidentiary scales in favor of Patent Owner on this issue.

Therefore, for the reasons given above, we determine Petitioner has proved by a preponderance of the evidence that dependent claims 3 and 4 of the ’592 patent are unpatentable as obvious under 35 U.S.C. § 103.

D. Ground 3: Asserted Obviousness of Claims 7–9 Over Winquist, the TROPIC Listing, and Mita

Petitioner argues that the pharmacokinetic (“PK”) profile limitations recited in dependent claims 7–9 of the ’592 patent would have been obvious to a POSA based on Winquist, the TROPIC Listing, and Mita. Pet. 40–41. Claims 7–9 each depend from claim 1. Petitioner notes that Mita expressly discloses the AUC and C_{max} concentrations recited in claims 7 and 8, respectively, and a plasma clearance rate that falls within the range recited in claim 9. *Id.* (citing Ex. 1002 ¶¶ 104, 145–148; Ex. 1012, 729). Petitioner argues that claims 7–9 recite pharmacokinetic parameters that are merely the result of administering cabazitaxel at a dose of 25 mg/m^2 every three weeks. *See* Ex. 1002 ¶ 56, discussing Ex. 1001, 18:36–49. As stated previously, Winquist and the TROPIC Listing together disclose administration of a 25 mg/m^2 intravenous dose of cabazitaxel every three weeks. The testimony of Dr. Seth supports a finding that such administration necessarily results in the PK profile distribution ranges recited in claims 7–9. Ex. 1009, 3948; Ex. 1002 ¶¶ 124–125.

Patent Owner does not address the substance of Ground 3 in its Response. *See* PO Resp. 21.

We agree with Petitioner’s argument and analysis and adopt the underlying evidence in support as our own fact findings. Pet. 40–41. Therefore, we determine Petitioner has proved by a preponderance of the evidence that dependent claims 7–9 of the ’592 patent are unpatentable as obvious under 35 U.S.C. § 103.

E. Asserted Obviousness of Dependent Claims 10, 11, 13, and 14

We first address claims 10 and 11, then turn our attention to claims 13 and 14.

1. Claims 10 and 11

Claim 10 depends from claim 1 and recites an additional method step of “monitoring blood counts and measuring neutrophil levels in the patient.” Claim 11 depends from claim 10 and adds “discontinuing cabazitaxel treatment in a patient with a neutrophil count of ≤1,500cells/mm^3.” Neutrophils are a type of white blood cell produced by bone marrow, and neutrophil counts are monitored during treatment. Ex. 1002 ¶ 61.

Petitioner argues that the subject matter of claims 10 and 11 would have been obvious over Winquist, the TROPIC Listing, and Tannock. Pet. 41–42. Patent Owner does not address the substance of claims 10 and 11 in its Response. *See* PO Resp. 21. We address Petitioner’s evidence below.

Tannock discloses the results of a phase III clinical study comparing administration of (i) docetaxel and prednisone with (ii) mitoxantrone and prednisone, in mCRPC patients. Ex. 1013, 1502–1503. Tannock teaches that neutrophil counts need to be monitored during therapy and a dose reduction or treatment delay should be implemented if the neutrophil count is less than 1,500 cells/mm^3. Ex. 1013, 1503 (Col. 2 ¶ 2)–1504 (Col. 2 ¶ 2); Ex. 1002 ¶ 150. 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, 1504 (Col. 2 ¶ 2).

Dr. Seth testifies that it was "well known in the art that administering taxanes to patients often results in reduced neutrophil counts, and that care must be taken to monitor neutrophil levels in patients undergoing chemotherapy with taxanes for this reason." Ex. 1002 ¶ 151 (referencing ¶¶ 61–62 and citing Ex. 1010, 1550 ("[n]eutropenia was the most common grade 3/4 hematological [adverse effect]" in administration of cabazitaxel.)). Dr. Seth further testifies that a POSA "would have readily appreciated the need to monitor neutrophil levels and discontinue or postpone treatment if they fell below 1,500 cells per cubic millimeter when administering a taxane, as taught by Tannock." *Id.* (citing Ex. 1013, 1503–1504). We credit Dr. Seth's testimony, which is fully supported by the teachings of Tannock. Therefore, we determine that it would have been obvious to a POSA in view of Tannock to monitor blood counts and measure neutrophil count levels during cabazitaxel therapy in accordance with Winquist and the TROPIC Listing, and to discontinue or postpone treatment if the neutrophil count was less than 1,500 cells/mm^{3}.

2. Claims 13 and 14

Claim 13 depends from claim 1 and recites a Markush group of corticoids "consisting of prednisone and prednisolone." Claim 14 depends from claim 13 and recites a corticoid dose of "10 mg/day." Petitioner argues that the subject matter of claim 13 would have been obvious over Winquist and the TROPIC Listing and the subject matter of claim 14 obvious over Winquist, the TROPIC Listing, and Tannock. Pet. 31, 42–43.

Patent Owner argues that Petitioner has not shown why a POSA would have used prednisone in combination with cabazitaxel, let alone at a dose of 10 mg/day. PO Resp. 45–46. We address the parties' arguments below.

Winquist and the TROPIC Listing expressly teach administering cabazitaxel in combination with prednisone, although a prednisone dose is not specified. Ex. 1009, 3948; Ex. 1008, 1. Dr. Seth testifies that combining taxanes, such as docetaxel, with prednisone for the treatment of prostate cancer was well known in the art. Ex. 1002 ¶ 62. Tannock teaches treating metastatic prostate cancer with docetaxel and prednisone, the prednisone being administered at a dose of 10 mg/day. Ex. 1013 at 1502, 1504 (Col. 1 ¶ 3). According to Tannock, a 10 mg/day dose of prednisone provides palliative care (pain relief) to some patients with prostate cancer. *Id*. at 1503 (Col. 1 ¶ 2); Ex. 1002 ¶ 153. Dr. Seth testifies that a POSA would have used the same 10 mg/day dose of prednisone described in Tannock to maintain palliative relief in mCRPC patients treated with cabazitaxel. Ex. 1002 ¶¶ 152–153.

Patent Owner invokes the risk of side effects from long-term corticosteroid use, the availability of alternatives to prednisone such as estramustine, and the availability of other prednisone dosing regimens to argue that the subject matter of claims 13 and 14 would not have been obvious to a POSA. PO Resp. 45–46. Dr. Sartor testifies that the only available data on the use of cabazitaxel in prostate cancer, reported in Attard and Mita, "was of cabazitaxel alone, not in combination with a corticoid." Ex. 2176 ¶ 176. Dr. Sartor further testifies that a POSA would have been aware that docetaxel in combination with estramustine "and without prednisone" was shown to have provided an overall survival benefit in mCRPC patients. *Id.* Dr. Sartor provides similar testimony regarding the use of mitoxantrone in combination with hydrocortisone. *Id.* ¶ 177. We are not persuaded by these arguments because Winquist and the TROPIC Listing disclose administration of cabazitaxel and *prednisone* to treat docetaxel-refractory mCRPC patients, not cabazitaxel and estramustine, cabazitaxel alone, or some other combination. *See* Ex. 1043 ¶ 11. In short, the combination treatment recited in claim 13 is expressly disclosed in the prior art.

We also are not persuaded that long-term side effects or the uncertainty of whether prednisone would provide a palliative benefit (Ex. 2176 ¶ 176) would have been sufficient for a POSA to override the express teaching of Winquist and the TROPIC Listing to administer cabazitaxel in combination with prednisone. As stated previously, Tannock taught that a 10 mg/day dose of prednisone provides palliative care (pain relief) to some patients with prostate cancer. Ex. 1013, 1503 (Col. 1 ¶ 2); Ex. 1002 ¶ 153. As Petitioner notes, Patent Owner's arguments are also undercut by prior art evidence of the routine administration of prednisone with mitoxantrone in post-docetaxel mCRPC patients. Ex. 1041, 235:2–236:4; Ex. 1043 ¶¶ 11–13; Ex. 2083, 307 (Col. 2 ¶ 2); Ex. 2111, 1, 9–12, 14, 27; Ex. 2176 ¶¶ 36, 38–39; Ex. 2177, 46:22–47:19. Therefore, we find a preponderance of the evidence establishes that it would have been obvious in view of Winquist, the TROPIC Listing, and Tannock for a POSA to treat docetaxel-refractory mCRPC patients with cabazitaxel in combination with 10 mg/day prednisone for palliative relief. Ex. 1002 ¶ 153.

For the reasons given above, we determine Petitioner has proved by a preponderance of the evidence that dependent claims 10, 11, 13, and 14 of the '592 patent are unpatentable as obvious under 35 U.S.C. § 103.

III. PATENT OWNER'S CONTINGENT MOTION TO AMEND

We have concluded that claims 1–5 and 7–30 of the '592 patent are unpatentable. Therefore, we address Patent Owner's contingent motion to enter proposed substitute claims 31–34. MTA 1, App. (claims 31–34). For the reasons that follow, Patent Owner's motion is denied.

As the moving party, Patent Owner bears the burden of proving patentability of each proposed substitute claim. 37 C.F.R. § 42.20(c); *see Nike, Inc. v. Adidas AG,* 812 F.3d 1326, 1334 (Fed. Cir. 2016) ("[T]he Board permissibly interpreted [37 C.F.R. § 42.20(c)] as imposing the burden of proving patentability of a proposed substitute claim on the movant: the patent owner."). Specifically, Patent Owner has the burden of proving that the substitute claims are patentably distinct over the prior art of record in the proceeding. *See Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1307–08 (Fed. Cir. 2015); *MasterImage 3D, Inc. v. RealD Inc.*, Case IPR2015–00040 (PTAB July 15, 2015) (Paper 42) (precedential); *Idle Free Systems, Inc. v. Bergstrom, Inc.*, Case IPR2012–00027 (PTAB June 11, 2013) (Paper 26) (informative); *but see In re Aqua Products*, No. 2015–1177, 2016 WL 4375651, at *1 (Fed. Cir. Aug. 12, 2016) (granting rehearing *en banc* to address burdens of persuasion and production regarding motions to amend under 35 U.S.C. § 316(d) and vacating *In re Aqua Products*, 823 F.3d 1369 (Fed. Cir. 2016)). For the reasons explained below, we conclude that Patent Owner has not met its burden with respect to the proposed substitute claims.

A. Proposed Substitute Claim 31

Proposed substitute claim 31 is reproduced below, with added text underlined and deleted text indicated by a single strike-through, followed by a clean version of the final claim language:

> 31. (substitute for Claim 27, if found unpatentable) A method of increasing [~~the~~] survival [~~of a patient~~] comprising administering to a patient in need thereof (i) an antihistamine, (ii) a corticoid, (iii) an H_2 antagonist, and (iv) a dose of 20 to 25 mg/m2 of cabazitaxel, or a hydrate or solvate thereof, wherein said antihistamine, said corticoid, and said H_2 antagonist are administered prior to said dose of 20 to 25 mg/m^2 of cabazitaxel, or hydrate or solvate thereof, in combination with prednisone or prednisolone, wherein said patient has [~~with a~~] castration resistant or hormone refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel [~~, comprising administering a dose of 20 to 25 mg/m2 of cabazitaxel, or a hydrate or solvate thereof, to the patient in combination with prednisone or prednisolone~~].

> 31. A method of increasing survival comprising administering to a patient in need thereof (i) an antihistamine, (ii) a corticoid, (iii) an H_2 antagonist, and (iv) a dose of 20 to 25 mg/m of cabazitaxel, or a hydrate or solvate thereof, wherein said antihistamine, said corticoid, and said H_2 antagonist are administered prior to said dose of 20 to 25 mg/m^2 of cabazitaxel, or hydrate or solvate thereof, in combination with prednisone or prednisolone, wherein said patient has castration resistant or hormone refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel.

MTA, App'x. Substitute claim 31, as compared to claim 27, still requires administering a dose of 20 to 25 mg/m^2 of cabazitaxel, or a hydrate or solvate thereof, in combination with prednisone or prednisolone to a patient with castration resistant or hormone refractory metastatic prostate cancer (mCRPC) that has progressed during or after treatment with docetaxel (docetaxel refractory). Substitute claim 31 amends the preamble to recite a "method of increasing survival" followed by "comprising administering to a patient in need thereof," the construction of which is disputed by the parties. MTA 1, 7–8; MTA Opp. 2–6; MTA Reply 1–3. Substitute claim 31 further limits original claim 27 by reciting the administration of an antihistamine, a corticoid, and an H_2 antagonist prior to administering the 20 to 25 mg/m^2 dose of cabazitaxel (hereafter "the premedication regimen"). MTA 2.

Patent Owner states that the proposed substitute claims add elements to claims 27–30 of the '592 patent and do not remove any limitations. *Id.* at 1–2. Therefore, Patent Owner contends, the proposed substitute claims are not broader than the original claims. *Id.*; 35 U.S.C. § 316(d)(3); 37 C.F.R. § 42.121(a)(2). We agree. The proposed substitute claims are not broader than claims 27–30, and Petitioner does not contend otherwise. *See generally* MTA Opp.

Substitute claims 32–34 depend directly from substitute claim 31, and they are substantively identical to original claims 28–30, except for substitute claim 33. *Id.* Substitute claim 33 is further amended to require that administration of the antihistamine, corticoid, and H_2 antagonist also occur as a new cycle every three weeks. *Id.* Patent Owner's proposed substitute claims 31–34 also represent a one-for-one substitution of original claims 27–30 in compliance with our rules. 37 C.F.R. § 42.121(a)(3).

B. Claim Construction

In inter partes review, the claims of an unexpired patent are interpreted using the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

We determine that only the following claim phrase requires explicit construction for purposes of deciding Patent Owner's contingent motion to amend claims 27–30. *See, e.g.*, *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

"A method of increasing survival comprising administering to a patient in need thereof"

Patent Owner argues that the preamble in substitute claim 31, "[a] method of increasing survival," is limiting as a "statement of intentional purpose for how the method is to be performed." MTA, 7 (citing *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003)). Patent Owner's claim construction attempts to tie "administering to a patient in need *thereof*" back to the preamble, such that the preamble means "a method that prolongs the life of a patient as compared to no treatment or palliative treatment." *Id.* at 8; MTA Reply 1. From this claim construction, Patent Owner argues the substitute claims are patentable because the prior art does not contain survival data necessary to teach a POSA that the claimed method would increase "overall survival" in docetaxel-refractory mCRPC patients. MTA 10–17. Patent Owner's claim construction and reliance on *Jansen* is misplaced.

Jansen is distinguishable from the present case because it was an infringement case that required the court to construe the subject claim "so as to sustain [its] validity, if possible." *Whittaker Corp. v. UNR Indus.*, 911 F.2d 709, 712 (Fed. Cir. 1990) (citing *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984)). In contrast, in an *inter partes* review, a claim must be given its broadest reasonable interpretation. In *Jansen*, moreover, the patent owner argued that the claimed method of treating anemia covered administration of the recited vitamin composition to those "in need thereof," which, according to the patent owner, meant "all people," i.e., even people who did not know they needed to prevent or treat anemia. *Jansen*, 342 F.3d at 1331, 1333–34. The court rejected patent owner's infringement contention and "strictly construed" the claims to define the patient population needing treatment, particularly in view of prosecution amendments that added the preamble and the "in need thereof" phrase to gain allowance of the claims. *Id.* The court concluded that the vitamin composition "must be administered to a human with a recognized need to treat or prevent macrocytic-megaloblastic anemia." *Id.* at 1334. In contrast, here, substitute claim 31 (and original claim 27) already defines a patient needing treatment in the body of the claim as a docetaxel-refractory mCRPC patient.

We agree with Petitioner's analysis that, in contrast to *Jansen*, to the extent "a patient in need thereof" refers to the preamble phrase "a method of increasing survival," it merely provides additional description of the patient in need of treatment, not some "intentional purpose" for how the treatment method is to be practiced in a defined patient population. MTA Opp. 3–4. *Jansen*, moreover, does not support Patent Owner's implicit proposal that the preamble imposes a claim requirement that the method must result in an increase in "overall survival" in a population of patients. *See, e.g.*, MTA 10 ("No Prior Art Disclosed or Suggested 20–25 mg/m^2 of Cabazitaxel . . . Would Increase Overall Survival."), 13 ("[P]hase I and II studies for cabazitaxel could not have determined whether cabazitaxel prolonged overall survival. . . . [T]umor responses and PSA reductions were not validated surrogates for overall survival in CRPC."). The preamble in substitute claim 31 describes a patient in need of "increasing survival"; it does not impose achieving a clinically-defined result of "overall survival" or "median survival" of a patient population. *See* Ex. 1001, 11:4–5 ("overall survival (OS): the time from inclusion [in] the study to the date of death"), 11:29–31 ("patients receiving cabazitaxel demonstrated statistically significant longer overall survival (OS) compared to mitoxantrone (p<0.0001)."), 11:35–37 ("The median survival for patients in the cabazitaxel group was 15.1 months in comparison to 12.7 months in the mitoxantrone group.").

Rapoport and *Glenmark* also do not support Patent Owner's proposed claim construction. MTA 7; MTA Reply 2. In *Rapoport*, there was no dispute that the preamble was a limitation of the treatment method ("limited to treatment of the underlying sleep apnea disorder itself"), because otherwise the claim term "'to a patient in need of *such treatment*' would not have proper antecedent basis." *Rapoport v. Dement*, 254 F.3d 1053, 1059 (Fed. Cir. 2001) (emphasis added). Limiting the claim to an intent to treat sleep apnea disorder itself, rather than more broadly encompassing treatment of anxiety secondary to sleep apnea, as proposed by patent applicant, was based on the specific language of the claim and specification at issue, which are distinguishable from the language of substitute claim 31. *Id.* at 1058–59. Similarly, the intent requirement in *Glenmark* was based on the specific language of that claim and preamble, which provided antecedent basis for several claim terms, and without which the claim lacked a complete description of the type of patient to be treated. *Sanofi v. Glenmark Pharms. Inc.*, No. 14-264, 2015 WL 5092631, at *10 (D. Del. Aug. 28, 2015).

Patent Owner also argues that the preamble is limiting because Patent Owner "relies on" increased survival to "distinguish prior art." MTA 8. Patent Owner, thus, invites the Board to treat its claim construction arguments prospectively as a prosecution disclaimer. However, "the PTO is under no obligation to accept a claim construction proffered as a prosecution history disclaimer." *Tempo Lighting, Inc. v. Tivoli, LLC*, 742 F.3d 973, 978 (Fed. Cir. 2014); *see also In re Lockwood*, 679 F. App'x 1021, 1027 (Fed. Cir. 2017) (quoting *Tempo Lighting*). We decline to do so here.

To the extent the preamble in substitute claim 31 may be considered limiting at all, it refers only to a patient in need of increased survival, i.e., a docetaxel-refractory mCRPC patient, the type of terminally-ill patient already defined in the body of the claim ("wherein said patient has castration resistant or hormone refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel"). *See* Ex. 1043 ¶ 10 ("one of the purposes of administering a taxane (such as docetaxel or cabazitaxel) to a patient with mCRPC that has progressed during or after docetaxel is to prolong the survival of that patient."); Ex. 2176 ¶¶ 35 ("mCRPC was an incurable condition; therefore, the goals of therapy were to . . . attempt prolongation of life."), 162 (same). As Dr. Sartor testified at deposition, "virtually all" docetaxel-refractory mCRPC patients are in need of a method of increasing survival. Ex. 1098, 431:4–17. Furthermore, as we stated in Section II.A.3., above, *Bristol-Myers Squibb* is relevant precedent and stands for the proposition that a method of treatment preamble stating the intended purpose of the treatment does not impose a result limitation on the recited method steps. *See* 246 F.3d at 1375–76 (affirming district court's construction of the method of treatment claims "as limited only to the actual steps of those claims, without regard to the result of performing the claimed steps"). Therefore, Patent Owner's argument that the preamble of substitute claim 31 imposes an "intentional purpose" or result ("overall survival") limitation on the recited method steps is unpersuasive and contrary to Federal Circuit precedent.

For the reasons given above, we decline to adopt Patent Owner's proposed claim construction.

C. Obviousness of the Substitute Claims

Patent Owner's nonobviousness argument comprises two components.

Patent Owner first argues, as previously noted, that the prior art does not disclose or suggest that 20–25 mg/m^2 of cabazitaxel in combination with prednisone or prednisolone would increase overall survival. MTA 10–18. Patent Owner's first argument is based on Patent Owner's proposed claim construction, which we have declined to adopt. The argument also reflects the errant approach of implicitly defining a reasonable expectation of "success" as requiring a clinically effective treatment, where *clinical results* establish an increase in overall survival in the context of a phase III clinical trial designed for FDA approval. *Id.* at 12–13 ("These references merely state that the primary endpoint of the TROPIC Study is overall survival. . . . However, no results of the [phase III] study were reported."), 13 ("[P]hase I and II studies for cabazitaxel could not have determined whether cabazitaxel prolonged overall survival"), 14 ("These [other CRPC] therapies . . . failed to prolong overall survival in phase III studies."), 16 ("Mita . . . and Pivot . . . failed to provide a POSA with a reasonable expectation that cabazitaxel therapy could prolong overall survival of mCRPC patients who had failed docetaxel therapy."). We again reject the argument for the same reasons given in Section II.B.4., above.

Patent Owner's second argument is that a POSA would not have been motivated to use the claimed premedication regimen prior to cabazitaxel therapy. *Id.* at 18–24. Patent Owner argues that a POSA would not have been so motivated because what was known about cabazitaxel therapy did not suggest "a concern over hypersensitivity reactions or fluid retention with respect to cabazitaxel administration." *Id.* at 19 (citing Ex. 2176 ¶¶ 241–245, 247, 250). Patent Owner further emphasizes a lack of motivation because the levels of hypersensitivity reactions and fluid retention observed in docetaxel and paclitaxel patients were "far greater" than those observed in cabazitaxel patients as reported in Mita and Pivot. *Id.* at 20–23 (citing Ex. 2176 ¶¶ 246, 249, 252–256). If anything, Patent Owner argues, the prior art teaches away from administering the claimed premedication regimen because of known side effects due to premedication with H_2 antagonists. *Id.* at 20, 23–24 (citing Ex. 2176 ¶¶ 257–262).

Petitioner persuasively establishes that the recited premedication regimen – administration of an antihistamine, a corticoid, and an H_2 antagonist – was well known as a prophylactic treatment for potential hypersensitivity reactions ("HSRs") in paclitaxel (Taxol) and docetaxel (Taxotere) therapies. MTA Opp. 10 (citing Ex. 1043 ¶¶ 44–46), 15–19 (citing Ex. 1043 ¶¶ 52–55, 64–69). We agree with Petitioner that a person of ordinary skill would have been motivated to use the same prior art taxane premedication regimen to decrease the risk of HSRs associated with cabazitaxel treatment. As Petitioner points out, Pivot reported a 4% rate of severe (grades 3–5) hypersensitivity reactions in metastatic breast cancer patients receiving cabazitaxel therapy after antihistamine (anti-H_1) pretreatment, a rate Dr. Sartor characterized as a "crazy high number." Paper 84 ("Observ.") ¶ 11 (citing Ex. 1041, 216:15–19); *see also* Ex. 1010, 1550 (Col. 2 ¶ 1), 1551 (Col. 2 ¶ 2). Therefore, although the rate of HSRs may have been lower when compared to paclitaxel and docetaxel therapy, we are persuaded a POSA still would have been motivated to prevent severe hypersensitivity reactions to cabazitaxel therapy by using a more thorough premedication regimen than the stand-alone antihistamine disclosed in Pivot. Ex. 1043 ¶¶ 64, 68–69.

An established taxane premedication regimen, comprising an antihistamine, corticoid, and H_2 antagonist used in connection with both paclitaxel (Taxol) and docetaxel (Taxotere) therapies, was known and available as a predictable use according to its established function of preventing or treating hypersensitivity reactions in prostate and breast cancer patients. *Id.*; *see KSR*, 550 U.S. at 420 (claimed subject matter may be proved obvious when "there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims."). The Taxol Label (paclitaxel) states that "to avoid the occurrence of severe hypersensitivity reactions, all patients treated with TAXOL should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine [an antihistamine] and H_2 antagonists (such as cimetidine or ranitidine)." Ex. 2093, 24; *see also id.* at 39. Dr. Sartor testified that this "broad type of regimen had been kicked around" by 2008 for use in taxane therapy. Ex. 1041, 211:22-23. Dr. Seth confirms the Taxol pretreatment regimen was known, and states that a POSA "would similarly be motivated to use the same three premedication drugs in cabazitaxel treatment of mCRPC as in paclitaxel treatments, to obtain a similar reduction in HSRs." Ex. 1043 ¶¶ 55, 64.

Patent Owner argues that the need for the Taxol pretreatment regimen was "attributable to the presence of Cremophor in the formulation" of Taxol. MTA 22–23 (citing Ex. 2093, 1, 27; Ex. 2089, 347; Ex. 2225, 18). However, multiple prior art references teach the use of the same Taxol pretreatment regimen to prevent HSRs in patients undergoing Taxotere (docetaxel) therapy, the formulation of which (like cabazitaxel) contains polysorbate 80 instead of Cremophor. MTA Opp. 15–16 (citing Ex. 1043 ¶¶ 53–54, 65–67; Ex. 1046; Ex. 1047; Ex. 1048). We discuss those references below.

Takenaka (Ex. 1046), published in 2008, describes a study administering 30 mg/m^2 docetaxel in combination with estramustine for the treatment of mCRPC. Ex. 1043 ¶ 52; Ex. 1046, 106. Takenaka states that "[d]examethasone 24 mg [a corticoid], diphenhydramine 50 mg [an antihistamine], and ranitidine 50 mg [H_2 antagonist] were administered before the [docetaxel] infusion to prevent a hypersensitivity reaction." Ex. 1046, 106 (Col. 2 ¶ 3); *see* Ex. 1001, 6:56–61, 7:15–21; Ex. 1043 ¶ 66. Notably, the full, three-part pretreatment regimen was indicated and used with a much lower docetaxel dose (30 mg/m^2) than the standard 75 mg/m^2 infusion dose indicated on the Taxotere label. Ex. 1024, 1. Takenaka's teaching to use the Taxol three-part pretreatment regimen (Ex. 2093, 24, 39) to prevent HSRs in low-dose docetaxel therapy, weighs against Patent Owner's argument that a POSA would not have used the pretreatment regimen with a 25 mg/m^2 dose of cabazitaxel because of a presumed lower concentration of polysorbate 80. Ex. 1043 ¶¶ 65–66.

Trudeau (Ex. 1047), published in 1996, reports that 60% of metastatic breast cancer patients experienced HSRs when docetaxel was administered without pretreatment, but "the use of a premedication regimen of oral dexamethasone and IV H_1 and H_2 blockers prevented significant HSRs." Ex. 1047, 422 (Col. 1 ¶ 3), 424 (Col. 2 ¶ 2); Ex. 1043 ¶¶ 53, 67. Hudis (Ex. 1048), also published in 1996, similarly reports on docetaxel treatment in metastatic breast cancer patients where, after observing two HSRs among the first six patients, "a variety of pretreatment regimens that incorporated diphenhydramine [an antihistamine], corticosteroids, and cimetidine [an H_2 blocker] were used." Ex. 1048, 59 (Col. 2 ¶ 4). Accordingly, we credit Dr. Seth's testimony that a POSA would have considered the use of the claimed pretreatment regimen of a corticosteroid, an antihistamine, and an H_2 antagonist as a well-known option for prevention of taxane-induced HSRs. Ex. 1043 ¶¶ 54, 65.

Patent Owner also contends that Mita would have taught away from using the claimed pretreatment regimen in connection with cabazitaxel therapy. MTA 19–20 (citing Ex. 1012; Ex. 2224, 2; Ex. 2176 ¶¶ 243–45, 248). Patent Owner relies on Mita's statement that "[b]ased on the results of this study, [cabazitaxel] does not require premedication, thus resulting in significant administration and convenience advantages." Ex. 1012, 729. Mita was a relatively small dosing and PK study, and Dr. Sartor's opinion states only that Mita "does not suggest that premedication was necessary for the safe administration of cabazitaxel." Ex. 2176 ¶ 251. Dr. Sartor does not state that Mita would have taught a POSA not to use a three-part premedication regimen, such as that used for the administration of paclitaxel and docetaxel, to prevent or treat HSRs in connection with cabazitaxel therapy.

Patent Owner's argument also does not address persuasively the larger phase II cabazitaxel study disclosed in Pivot, which used an antihistamine pretreatment. MTA 19–20. Notwithstanding the earlier statement in Mita, Pivot teaches the use of an antihistamine pretreatment regimen in an effort to reduce allergic reactions. Ex. 1010, 1548 (Col. 2 ¶ 3). Pivot discloses that when administering cabazitaxel, the most common grade 3–5 non-hematological adverse event was HSR. *Id.* at 1550. Dr. Seth states that a 4% rate of serious (grade 3 or higher) HSRs would be of concern to a POSA and would warrant the use of the claimed pretreatment regimen. Ex. 1043 ¶ 68. Furthermore, Pivot discloses one patient withdrawal due to "grade 4 allergic reaction." Ex. 1010, 1550 (Col. 2 ¶ 2). The grade 4 allergic reaction "would certainly qualify as an HSR," and prevention of such allergic reactions "would be a strong motivation to use a paclitaxel-type regimen of an antihistamine, a corticoid, and an H_2 antagonist." Ex. 1043 ¶ 68. Accordingly, when Mita is put in context with the Pivot study, we are persuaded Mita does not teach away from the use of the claimed premedication regimen to mitigate HSRs in patients receiving cabazitaxel therapy.

Dr. Sartor agrees that a 4% rate of grade 3 or higher HSRs would have been serious enough to merit the use of preventative premedication. Ex. 1041, 215:6–216:19. Dr. Sartor explains that, when considering premedication for taxanes, preventing HSRs is of paramount concern: "I think when you're looking at safety, you really want to be very cautious because, I mean, the last thing you want to do is give the drug to somebody and they have a hypersensitivity reaction and die. And that's a true disaster." *Id.* at 211:23–212:4. In particular, the HSR rate disclosed by Pivot (4%) would provide a strong motivation to use premedication, because, as Dr. Sartor explains, "4 percent of people with a bad hypersensitivity is a crazy high number, scares the hell out of me." *Id.* at 216:15–19. Dr. Sartor further explains that none of the claimed premedication drug products are dangerous:

> Q. Aren't H_2 antagonists extremely risky medications?
> A. No. Why would you say that?
>
> Q. What about Benadryl? Is that an extremely risky medication?
> A. No.
>
> Q. What about dexamethasone?
> A. In the way we use it, it's not extremely risky. And it's all about the risk/benefit anyway. We always incur risks. We're going to incur risks when we go get on the elevator.

> But, you know, it's about the proper amount of risk and the benefit that it can be prescribed. Hypersensitivity reactions -- I don't want to be too distracting, but I had a guy nearly die. … Anyway, the bottom line is it's a serious matter because we're talking about real health here. When I look at the safety of Benadryl, I've had people get sleepy on Benadryl. I've never had any real harm done.

Id. at 217:20–219:5. Dr. Sartor also testified that "when we administer an agent known to be associated with hypersensitivity reactions, if there's a method to help control those, then we use that." *Id*. at 211:5–8. Thus, Dr. Sartor's testimony weighs against Patent Owner's teaching away argument and tends to confirm that preventing HSRs in patients receiving cabazitaxel therapy would have motivated a POSA to practice the method of the substitute claim, including the known taxane premedication regimen, with a reasonable expectation of success.

Accordingly, the administration of the premedication regimen when administering cabazitaxel and prednisone for treating mCRPC patients, as recited in substitute claims 31–34, would have been obvious to a POSA in view of the Winquist, the TROPIC Listing, Pivot, and any one of Takenaka, Hudis, Trudeau, and the Taxol Label. Ex. 1043 ¶ 68.

For the reasons given above, we determine Patent Owner has not proved by a preponderance of the evidence that proposed substitute claims 31–34 are patentable.

IV. MOTIONS TO EXCLUDE

Petitioner and Patent Owner each move to exclude certain evidence.

Patent Owner filed a Motion to Exclude Exhibits 1089–1090. Paper 61. Petitioner filed an Opposition (Paper 77 (under seal), Paper 78 (public version)), and Patent Owner filed a Reply (Paper 86). Exhibit 1089 is titled "Cabazitaxel IMS 2009-10 DollarsDoses (Confidential)," and Exhibit 1090 is titled "Cabazitaxel IMS 2011-16 DollarsDoses (Confidential)." These exhibits are cited in Mr. McSorley's Declaration in connection with sales figures, in dollars and prescriptions, of prostate cancer drugs. Ex. 1044, 105–120. Mr. McSorley relies on Exhibits 1089 and 1090 for his Attachments 7.0–7.7 and 8.0–8.7, which are cited in Exhibit 1044 at ¶¶ 24–27, 48, 53, 57–58, 70.A (Figure H), 71.A (Figure I), 74.

We do not rely on Exhibit 1089 or Exhibit 1090, or on Mr. McSorley's Declaration in connection with Exhibits 1089 or 1090 to support our decision. Therefore, Patent Owner's Motion to Exclude Exhibits 1089 and 1090 is denied as moot.

Petitioner filed a Motion to Exclude Exhibits 2170, 2171, and 2179 and certain related paragraphs in Mr. Tate's Declaration, Exhibit 2149. Paper 64 (under seal); Paper 68 (public version). Patent Owner filed an Opposition (Paper 72 (under seal), Paper 73 (public version)), and Petitioner filed a Reply (Paper 89 (under seal), Paper 95 (public version)). The exhibits are described as "Market Share with Docetaxel in Prior Treatment, Brand Impact by Alpha Impact Rx (June 2016)" (Ex. 2170), "Monthly Jevtana Prostate Cancer Treatment Report: August 2014 Results, BrandImpact by AlphaImpact Rx and Symphony Health Solutions

(September 2014)" (Ex. 2171), and "Underlying data for Market Share with Docetaxel in Prior Treatment, BrandImpact by AlphaImpact Rx (June 2016)" (Ex. 2179). Mr. Tate references the exhibits in connection with sales and market share data in support of Patent Owner's commercial success argument. For the reasons explained in Section II.B.4.d., above, we do not address the substance of Exhibits 2170, 2171, 2179 or the related paragraphs of Mr. Tate's Declaration in our decision. Therefore, Petitioner's Motion to Exclude Exhibits 2170, 2171, 2179, and the related paragraphs in Exhibit 2149 is denied as moot.

Petitioner also moves to exclude certain paragraphs of Dr. Sartor's original declaration filed in support of Patent Owner's Preliminary Response (Ex. 2001) and his Declaration filed in support of Patent Owner's Response and MTA (Ex. 2176). Paper 64, 14–15. We do not rely on or reference Exhibit 2001 in our decision. Therefore, Petitioner's Motion to Exclude paragraphs 83 and 98 of Exhibit 2001 is denied as moot.

Petitioner contests the admissibility of paragraphs 63, 65, 90, 103–110, 152, 155, 167, and 207 of Exhibit 2176. We do not reference paragraphs 63, 65, 90, 103–109, 152, 155, or 167 in this Decision. Therefore, Petitioner's motion as to those paragraphs is denied as moot.

To the extent we reference paragraphs 110 and 207 of Exhibit 2176 in this Decision, the citations are only for purposes of setting out Patent Owner's position. We do not address the substance of the testimony in those paragraphs. Therefore, Petitioner's Motion to Exclude paragraphs 110 and 207 of Exhibit 2176 is denied as moot.

V. CONCLUSION

For the reasons given above, we determine Petitioner has shown by a preponderance of the evidence that claims 1–5 and 7–30 of the ’592 patent are unpatentable.

We further determine Patent Owner has not proved by a preponderance of the evidence that proposed substitute claims 31–34 are patentable. Therefore, Patent Owner’s Contingent Motion to Amend claims 27–30 with proposed substitute claims 31–34 is *denied*.

We further deny the parties’ motions to exclude evidence as moot.

This is a Final Written Decision. Parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

VI. ORDER

Accordingly, it is

ORDERED that claims 1–5 and 7–30 of the ’592 patent have been proved to be unpatentable by a preponderance of the evidence;

FURTHER ORDERED that proposed substitute claims 31–34 have not been shown to be patentable. Therefore, Patent Owner’s Contingent Motion to Amend claims 27–30 with proposed substitute claims 31–34 is denied.

For PETITIONER:

Steven W. Parmelee
Michael T. Rosato
Jad A. Mills
Wendy Devine
Matthew Reed
Nellie Amjadi
WILSON SONSINI GOODRICH & ROSATI
sparmelee@wsgr.com
mrosato@wsgr.com
jmills@wsgr.com
wdevine@wsgr.com
mreed@wsgr.com
namjadi@wsgr.com

For PATENT OWNER:

Dominic A. Conde
Whitney L. Meier
William E. Solander
Joshua I. Rothman
FITZPATRICK CELLA HARPER & SCINTO
dconde@fchs.com
wmeier@fchs.com
wsolander@fchs.com
jrothman@fchs.com