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Paper 84
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC., ACTAVIS LABORATORIES FL, INC., AMNEAL PHARMACEUTICALS LLC, AMNEAL PHARMACEUTICALS OF NEW YORK, LLC, DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., SUN PHARMACEUTICALS INDUSTRIES, LTD., SUN PHARMACEUTICALS INDUSTRIES, INC., TEVA PHARMACEUTICALS USA, INC., WEST-WARD PHARMACEUTICAL CORP., and HIKMA PHARMACEUTICALS, LLC,
Petitioner,

v.

JANSSEN ONCOLOGY, INC.,
Patent Owner.

Case IPR2016-01332[1]
Patent 8,822,438 B2

Before LORA M. GREEN, RAMA G. ELLURU, and KRISTINA M. KALAN, *Administrative Patent Judges*.

KALAN, *Administrative Patent Judge.*

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

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[1] Case IPR2017-00853 has been joined with this proceeding.

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Mylan") filed a Petition (Paper 1, "Pet.") to institute an *inter partes* review of claims 1–20 of U.S. Patent No. 8,822,438 B2 (Ex. 1001, "the '438 patent") pursuant to 35 U.S.C. §§ 311–319. Janssen Oncology, Inc. ("Patent Owner") filed a Preliminary Response (Paper 14, "Prelim. Resp."). We instituted an *inter partes* review of claims 1–20 on certain grounds of unpatentability alleged in the Petition (Paper 21, "Dec.").

Actavis Laboratories FL, Inc., Amneal Pharmaceuticals LLC, Amneal Pharmaceuticals of New York, LLC, Dr. Reddy's Laboratories, Inc., Dr. Reddy's Laboratories, Ltd., Sun Pharmaceuticals Industries, Ltd., Sun Pharmaceuticals Industries, Inc., Teva Pharmaceuticals USA, Inc., West-Ward Pharmaceutical Corp., and Hikma Pharmaceuticals, LLC (collectively, the "Actavis Petitioners") filed a Petition for *inter partes* review of claims 1–20 of the '438 patent. Case IPR2017-00853, Paper 8. Together with its Petition, the Actavis Petitioners filed a Motion for Joinder to join the case with the previously instituted proceeding in IPR2016-01332. *Id.*, Paper 9. We instituted trial in IPR2017-00853 and joined the Actavis Petitioners as a Petitioner in IPR2016-01332. *Id.,* Paper 19.

After institution of trial, Patent Owner filed a Patent Owner Response (Paper 35, "PO Resp."). Mylan and the Actavis Petitioners (collectively, "Petitioner") filed a Reply (Paper 55, "Reply"). Pursuant to a Board Order (Paper 64), Patent Owner filed an Identification of New Arguments and Evidence in Petitioner's Reply (Paper 65), to which Petitioner filed a Reply

(Paper 74). An oral hearing was held on May 24, 2017. A transcript of the hearing has been entered into the record. Paper 82 ("Tr.").

The Board has jurisdiction under 35 U.S.C. § 6. In this Final Written Decision, issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73, we determine that Petitioner has shown by a preponderance of the evidence that all claims of the '438 patent for which trial was instituted, namely, claims 1–20, are unpatentable.

II. BACKGROUND

A. Related Matters

The parties indicate that the '438 patent is being asserted in a number of district court proceedings, some of which have been terminated. Pet. 1–2; Paper 7, 3. Patent Owner represents that the following proceedings have not been terminated: *BTG Int'l Ltd. v. Actavis Labs. FL, Inc.,* C.A. No. 2:15-cv-05909-KM-JBC (D.N.J.); and *Janssen Biotech, Inc. v. Mylan Pharms. Inc.,* C.A. No. 1:15-cv-00130-IMK (N.D. W. Va.), *BTG Int'l Ltd. v. Amerigen Pharms., Inc.,* C.A. No. 2:16-cv-02449-KM-JBC (D.N.J.); and *BTG Int'l Ltd. v. Glenmark Pharms. Inc., USA*, C.A. No. 2:16-cv-5909 (D.N.J). Paper 27, 3.

Patent Owner also states that the '438 patent was the subject of *ex parte* reexamination request No. 90/020,096, but "will not be granted a filing date for failure to comply with the requirements of 37 C.F.R. § 1.501(a)." Paper 7, 2.

B. The '438 Patent

The '438 patent, titled "Methods and Compositions for Treating Cancer," describes methods that comprise "administering a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor, such as abiraterone acetate (i.e., 3β-

acetoxy-17-(3-pyridyl)androsta-5,16-diene), in combination with at least one additional therapeutic agent such as an anti-cancer agent or a steroid." Ex. 1001, at [54], [57]. As described in the '438 patent, it is believed that testosterone and dihydrotestosterone promote the growth of prostate cancer. *Id.* at 1:49–51. Hormone therapy can be used to suppress the production or block the effects of hormones such as testosterone. *Id.* at 1:43–51.

The enzyme 17α-hydroxylase/$C_{17, 20}$-lyase ("CYP17") is involved in testosterone synthesis. *Id.* at 3:66–4:1. CYP17 inhibitors have been shown to be useful in the treatment of cancer, specifically, androgen-dependent disorders like prostate cancer. *Id.* at 5:23–27. Abiraterone acetate, a prodrug of abiraterone, is a CYP17 inhibitor. *Id.* at 2:10–12.

The '438 patent describes administration of a therapeutically effective amount of a CYP17 inhibitor, such as abiraterone acetate, with a therapeutically effective amount of at least one additional therapeutic agent including, but not limited to, an anti-cancer agent, such as mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, or flutamide, or a steroid, such as hydrocortisone, prednisone, or dexamethasone. *Id.* at 2:9–3:20.

C. Challenged Claims

Claim 1 of the '438 patent is reproduced below:

> 1. A method for the treatment of a prostate cancer in a human comprising administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of prednisone.

Ex. 1001, 16:16–20. Dependent claims 2–20 of the '438 patent describe additional limitations of the method, including the amount of abiraterone

acetate and the amount of prednisone used and the type of prostate cancer being treated. *Id.* at 16:21–17:14.

D. Prior Art References Relied Upon by Petitioner

Petitioner relies on the following prior art:

1. O'Donnell, A. et al., *Hormonal impact of the 17α-hydroxylase/ $C_{17,20}$-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer*, 90 British Journal of Cancer 2317–25 (2004) ("O'Donnell") (Ex. 1003);
2. Gerber, G.S. & Chodak, G.W., *Prostate specific antigen for assessing response to ketoconazole and prednisone in patients with hormone refractory metastatic prostate cancer*, 144 J. Urol. 1177–79 (1990) ("Gerber") (Ex. 1004); and
3. U.S. Patent No. 5,604,213 to Barrie, issued February 18, 1997 ("Barrie") (Ex. 1005).

E. Instituted Grounds of Unpatentability

We instituted *inter partes* review of claims 1–20 of the '438 patent on the following grounds:

References	**Basis**	**Claims Challenged**
O'Donnell and Gerber	§ 103	1–20
Barrie and Gerber	§ 103	1–4 and 6–11

In support of its challenges, Petitioner relies on the declarations of Marc B. Garnick, M.D. (Ex. 1002; Ex. 1104, 1153), Ivan T. Hoffman (Ex. 1017; Ex. 1134, 1146, 1151, 1154), Ian McKeague, Ph.D. (Ex. 1091), John Bantle, M.D. (Ex. 1097) and Bryan D. Beel (Ex. 1152). Patent Owner relies on the declarations of Ian Judson, M.D. (Ex. 2028), Matthew Rettig, M.D. (Ex. 2038), Richard Auchus, M.D., Ph.D. (Ex. 2040), Christopher A. Vellturo, Ph.D. (Ex. 2044), and Johann S. De Bono (Ex. 2118).

III. ANALYSIS

A. Claim Interpretation

The Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard); 37 C.F.R. § 42.100(b). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Only those terms which are in controversy need to be construed, and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("we need only construe terms 'that are in controversy, and only 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)).

With respect to claim interpretation, "[u]sually [the specification] is dispositive; it is the single best guide to the meaning of a disputed term." *In re Abbott Diabetes Care Inc.*, 696 F.3d 1142, 1149 (Fed. Cir. 2012) (citations omitted). "To act as its own lexicographer, a patentee must 'clearly set forth a definition of the disputed claim term' other than its plain and ordinary meaning." *Thorner v. Sony Computer Entm't Am. LLC,* 669 F.3d 1362, 1365

(Fed. Cir. 2012) (quoting *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002)).

Petitioner proposes that we construe the claim terms "treat," "treating," "treatment," "anti-cancer agent," and "refractory cancer." Pet. 17–19. We adopted constructions for these claim terms in the Decision on Institution in IPR2016-00286.[2] Pet. 18 (citing IPR2016-00286, Paper 14). In our Decision on Institution in IPR2016-00286, we construed those terms, as well as the term "therapeutically effective amount of prednisone" as follows:

Claim term(s)	**Construction**
"treat," "treating," and "treatment"	include the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer Ex. 1001, 3:46–50
"anti-cancer agent"	any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits, stops or reduces the proliferation of cancer cells Ex. 1001, 4:8–16
"refractory cancer"	cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment Ex. 1001, 4:23–27.
"therapeutically effective amount of prednisone"	an amount of prednisone effective for treating prostate cancer

[2] IPR2016-00286 is an earlier-filed case involving the '438 patent, the same grounds, and the same Patent Owner. Petitioner filed a motion for joinder of this case with IPR2016-00286 (Paper 3), which we denied (Paper 21).

Patent Owner, in its Response, states: "The Panel's construction of 'treat,' 'treating' and 'treatment' is consistent with the disclosure of the '438 patent and should be maintained." PO Resp. 6. Patent Owner also states that it "understands the Panel's construction to mean that administration of prednisone with abiraterone acetate, must *at least* cause an anti-cancer effect, regardless of whether it has any other non-anti-cancer effects." *Id.* at 5. Petitioner replies that "the Board clearly held that 'treatment' does not require an antitumor or anticancer effect." Reply 18 (citing IPR2016-00286, Decision on Institution (Paper 14) at 5; IPR2016-00286, Decision Denying Request for Rehearing (Paper 23) at 3 (rejecting Janssen's request for rehearing and noting that the Board's construction of "treating" does not require "having an anti-cancer effect on").)

Patent Owner also submitted a claim construction of the terms "treatment" and "treating" by the district court in a companion litigation. Ex. 2004. The district court, after a lengthy analysis, construed the disputed terms as follows: "*Treatment/treating* means the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer." *Id.* at 30. The district court read out of the definition the term "includes." *Id.* Although we are not bound by the district court's reasoning and claim constructions in related proceedings, we do not disregard the determinations of a court interpreting the same claim term in a related patent in a concurrent proceeding. *Power Integrations, Inc. v. Lee*, 797 F.3d 1318, 1326–27 (Fed. Cir. 2015) ("The fact that the board is not generally bound by a previous judicial interpretation of a disputed claim term does not mean, however, that it has no obligation to acknowledge that interpretation or to

assess whether it is consistent with the broadest reasonable construction of the term."). Thus, although we acknowledge and have considered the district court's interpretation, we retain our broadest reasonable construction of the terms "treat," "treatment," and "treating."

We see no reason to modify our claim construction positions in light of the record developed at trial, and we maintain our claim constructions from the Decision on Institution for the purposes of this Decision. No other claim terms have been presented to us for construction following institution of trial, and we determine that no other claim terms require express construction.

B. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103[3] if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A decision on the ground of obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion of

[3] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. § 103. Because the '438 patent has an effective filing date before the effective date of the applicable AIA amendments, throughout this Decision we refer to the pre-AIA versions of 35 U.S.C. § 103.

obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The obviousness analysis "should be made explicit" and it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at 418. We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

C. Level of Skill in the Art

We adopt Petitioner's contention that a person of ordinary skill in the art

> would be a physician specializing in urology, endocrinology, or oncology, or a person holding a Ph.D. in pharmacology, biochemistry or a related discipline, such as pharmaceutical science. Additional experience could substitute for the advanced degree. To the extent necessary, one of skill in the art may collaborate with one or more other persons of skill in the art for one or more aspects with which the other person may have expertise, experience and/or knowledge that was obtained through his or her education, industrial or academic experiences. For example, one of skill may consult with an endocrinologist, oncologist, or medical biochemist and thus may rely on the opinions of such specialists in evaluating the claims.

Pet. 7 (citations omitted). Patent Owner does not appear to dispute Petitioner's definition in its Patent Owner Response. *See generally* PO Resp. The level of ordinary skill in the art in this case is further demonstrated by the prior art asserted in the Petition. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

D. Overview of the Prior Art

1. O'Donnell

O'Donnell, which is titled "Hormonal impact of the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer," discloses that treatment of prostate cancer with abiraterone acetate, at a dose of 500–800 mg, can successfully suppress testosterone levels. Ex. 1003, Abstract. O'Donnell also discloses that ketoconazole, another CYP17 inhibitor, has been evaluated as a possible agent with which to achieve decreased production of adrenal steroids, but that abiraterone acetate was developed as a more selective inhibitor. *Id.* at 2318. O'Donnell further discloses that adrenocortical suppression may require administration of replacement glucocorticoid. *Id.* at Abstract, 2323. O'Donnell states that "[s]ome impact on adrenal reserve was predictable from the steroid synthesis pathway." *Id.* at 2323. Regarding administration of ketoconazole, O'Donnell states that "it is common practice to administer supplementary hydrocortisone" and that this may prove necessary with abiraterone acetate. *Id.* On the basis of the clinical evidence, O'Donnell reports that the need for concomitant therapy of abiraterone acetate with a glucocorticoid needs to be further investigated. *Id.*

2. Gerber

Gerber, which is titled "Prostate Specific Antigen for Assessing Response to Ketoconazole and Prednisone in Patients with Hormone Refractory Metastatic Prostate Cancer," discloses use of ketoconazole, a known CYP17 enzyme inhibitor and inhibitor of gonadal and adrenocortical steroid synthesis, with prednisone to treat patients with progressive prostate cancer. Ex. 1004, 1177. Gerber provides that patients exhibiting

progressively increasing prostate specific antigen ("PSA") levels, when treated with ketoconazole and prednisone, experienced a decrease in PSA levels. *Id.* at 1178–79. Based on its study, Gerber concludes that "there appears to be a small subgroup of patients with progressive prostate cancer despite hormonal therapy who will derive significant benefit from the combination of ketoconazole and glucocorticoid replacement therapy." *Id.* at 1179.

3. Barrie

Barrie, which is titled "17-Substituted Steroids Useful in Cancer Treatment," is directed to a class of 17-substituted steroids and their use in the treatment of androgen-dependent and estrogen-dependent disorders. Ex. 1005, 1:11–14. Specifically, Barrie discloses abiraterone, acid addition salts and 3-esters of abiraterone, and abiraterone acetate. *Id.* at 5:21–26, 7:23–26, 11:39–55. Barrie discloses that abiraterone acetate may be administered in a method of treating disorders, including prostate cancer, as a pharmaceutical composition comprising a therapeutically effective amount of abiraterone acetate. *Id.* at 10:27–57. Barrie compares the inhibition levels of hormone production by abiraterone acetate with ketoconazole, concluding that the decrease in testosterone levels resulting from administration of abiraterone acetate was much more marked than for ketoconazole. *Id.* at 26:32–38.

E. Obviousness Analysis

1. Petitioner's Arguments

Petitioner argues, generally, that it was "known that in using a CYP17 inhibitor to reduce testosterone synthesis, the CYP17 inhibitor also undesirably suppressed the production of cortisol, a glucocorticoid, which is

necessary for other biochemical cycles in the body." Pet. 5. In particular, reduced production of cortisol "caused adverse effects, including hypertension, hypokalemia (decrease in circulating potassium levels), and fluid retention." *Id.* (citing Ex. 1002 ¶¶ 42, 44, 58). Administration of a CYP17 inhibitor to suppress androgen synthesis results in the "undesired side effect" that "cortisol production is compromised (*e.g.,* reduced), which interferes with the negative feedback mechanism that usually maintains cortisol levels within the normal physiological range." *Id.* at 26. Petitioner also argues that it was "known that CYP17 inhibition of cortisol increased ACTH drive (*i.e.*, increased ACTH production), which resulted in a corresponding increase in mineralocorticoids," leading to mineralocorticoid excess. *Id.* at 27 (citing Ex. 1002 ¶ 41). It was general knowledge in the art, Petitioner argues, "to administer a glucocorticoid, such as prednisone or hydrocortisone, to a patient with ACTH drive, such as a patient administered a CYP17 inhibitor, to reduce ACTH drive, and consequently, reduce mineralocorticoid excess." *Id.* (citing Ex. 1002 ¶ 42).

a. Ground Based on O'Donnell and Gerber

Petitioner challenges claims 1–20 as obvious under 35 U.S.C. § 103 over O'Donnell and Gerber. Pet. 38–50.

Regarding claim 1, Petitioner argues that O'Donnell teaches "that abiraterone acetate is a selective CYP17 inhibitor that is more effective than ketoconazole, a CYP17 inhibitor known in the art, in suppressing testosterone levels in a mammal *in vivo*." Pet. 38 (citing Ex. 1003, 2138, 2322, 2323, 2325). Petitioner further argues that, although O'Donnell does not disclose administration of abiraterone acetate with prednisone, "O'Donnell taught that concomitant hormone replacement therapy with a glucocorticoid may be

needed when using abiraterone acetate to treat a prostate cancer in a human patient." *Id.* at 39 (citing Ex. 1003, 2323). Gerber, Petitioner argues, teaches that "the combination of ketoconazole and prednisone (a glucocorticoid) is safe and effective in treating human patients with hormone-refractory advanced prostate cancer." *Id.* at 39–40 (citing Ex. 1005 [sic], 1177–79).

Regarding motivation to combine, Petitioner reasons that one of skill in the art "would have been motivated to add prednisone to a method of using abiraterone acetate (a CYP17 inhibitor)" to treat prostate cancer in a human patient "by Gerber's teaching that administering 5 mg prednisone twice daily with ketoconazole, also a CYP17 inhibitor, is a safe and effective treatment in human patients with hormone-refractory prostate cancer." *Id.* at 40. Petitioner also argues that one of ordinary skill in the art would have been "motivated by suggestions in the prior art that prednisone could have some amount of anti-cancer activity." *Id.* (citing Ex. 1002 ¶¶ 33, 89–90). Overall, Petitioner argues, one of ordinary skill in the art would have combined abiraterone acetate and prednisone "with a reasonable expectation of success" because the "prior art taught that abiraterone acetate was a more effective CYP17 inhibitor than ketoconazole and that the combination of ketoconazole and prednisone was safe and effective to treat patients with hormone refractory metastatic prostate cancer, which would have motivated the combination." *Id.* at 6 (citing Ex. 1002 ¶¶ 55–59).

Claims 2–20 each depend directly or indirectly from claim 1. Petitioner contends these claims are also unpatentable under 35 U.S.C. § 103 based on O'Donnell and Gerber. Pet. 42–50.

b. Ground Based on Barrie and Gerber

Petitioner challenges claims 1–4 and 6–11 as obvious under 35 U.S.C. § 103 over Barrie and Gerber. Pet. 38–47.

Regarding claim 1, Petitioner argues that Barrie teaches "that abiraterone acetate is a selective CYP17 inhibitor that is more effective than ketoconazole, a CYP17 inhibitor known in the art, in suppressing testosterone levels in a mammal *in vivo*." Pet. 38 (citing Ex. 1005, 25:13–26:63). Gerber, Petitioner argues, teaches that "the combination of ketoconazole and prednisone (a glucocorticoid) is safe and effective in treating human patients with hormone-refractory advanced prostate cancer." *Id.* at 39–40 (citing Ex. 1005 [sic], 1177–79).

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hormone refractory metastatic prostate cancer, which would have motivated the combination." *Id.* at 6 (citing Ex. 1002 ¶¶ 55–59).

Claims 2–4 and 6–11 each depend directly or indirectly from claim 1. Petitioner contends these claims are also unpatentable under 35 U.S.C. § 103 based on Barrie and Gerber. Pet. 42–47.s

2. Patent Owner's Non-Obviousness Arguments

Patent Owner presents a series of arguments directed to the art relied upon in both of Petitioner's grounds, arguments directed to the reasons to combine the prior art, and arguments related to objective indicia of non-obviousness. PO Resp. 10–64. We address each in turn.

a. Patent Owner's First Argument

Patent Owner argues, first, that Petitioner's "obviousness theory is anchored on its assertion that, because abiraterone acetate and ketoconazole are both 'CYP17 inhibitors,' they will cause the same side effects." PO Resp. 13. Rather, Patent Owner argues, abiraterone acetate and ketoconazole cause very different effects on steroid biosynthesis. *Id.* (citing Ex. 2126, 29:5–17; 8:5–21). Patent Owner emphasizes that ketoconazole "is considered a *non-selective* steroid synthesis inhibitor" whereas abiraterone acetate "is a *selective* CYP17 inhibitor" that targets only CYP17. *Id.* at 13–15, Figs. 1, 2 (citing Ex. 2038 ¶¶ 19–20, 25–39, 97, 103). Patent Owner faults Petitioner's expert for omitting "any mention of these fundamental differences in the effects of ketoconazole and abiraterone acetate on the various steroid synthesis pathways, particularly those that might implicate a need for glucocorticoid replacement therapy." *Id.* at 17.

Patent Owner argues, next, that Petitioner incorrectly contends that ketoconazole and abiraterone acetate cause the same side effects. *Id.* Rather,

Patent Owner argues, there is no prior art evidence that ketoconazole causes mineralocorticoid excess. *Id.* at 18. According to Patent Owner, "mineralocorticoid production was *reduced* in patients administered ketoconazole." *Id.* (citing Ex. 2040 ¶ 38; Ex. 2067, 585). Patent Owner further argues that there was no evidence in 2006 that abiraterone acetate would cause mineralocorticoid excess. *Id.* at 19 (citing Ex. 2038 ¶¶ 154–60, 162; Ex. 2040 ¶¶ 49–66). Neither Barrie nor O'Donnell, Patent Owner notes, measures mineralocorticoid excess. *Id.* at 19–20.

Petitioner replies that ketoconazole and aminoglutethimide, known treatments for prostate cancer, inhibited production of testosterone and numerous other steroids such as cortisol, resulting in conditions such as mineralocorticoid excess and adrenal insufficiency and symptoms such as hypertension, hypokalemia, fluid retention, fatigue, nausea and vomiting, weight loss, and hypotension. Reply 4–5 (citing Ex. 1097 ¶¶ 32–33, 37–39, 41; Ex. 1104 ¶¶ 16–23). Abiraterone acetate, as a "next generation steroid synthesis inhibitor," is in the same class of treatment agents as ketoconazole and aminoglutethimide, argues Petitioner, and therefore, "a skilled artisan would have been concerned that abiraterone acetate would induce similar side effects as other steroid synthesis inhibitors." *Id.* at 5–6 (citing Ex. 1104 ¶¶ 14–31, Ex. 1097 ¶¶ 44–49). Thus, "in light of steroid synthesis inhibitors' known effects on the adrenal pathways, a skilled artisan would have been motivated to administer glucocorticoids with abiraterone acetate to counteract expected endocrine disruptions." *Id.* at 7 (citing Ex. 1097 ¶¶ 21–66, Ex. 1104

¶¶ 20–22, 40–79). Petitioner also argues that O'Donnell's test results were consistent with mineralocorticoid excess. *Id.* at 15.

Based on the information presented during trial, we understand that ketoconazole and abiraterone acetate do not have identical mechanisms. *See, e.g.,* Ex. 2038 ¶¶ 25–39, Figs. 4, 5). As noted by both Petitioner and Patent Owner, however, abiraterone acetate and ketoconazole are both steroid synthesis inhibitors, particularly, CYP17 inhibitors. Pet. 26; PO Resp. 13–15; Reply 2, 5, 9. Both parties appear to agree that, based on their respective mechanisms of action, administration of ketoconazole would inhibit production of cortisol, and administration of abiraterone acetate inhibits one of the pathways of cortisol production. Pet. 5, 26; Tr. 12:18–19; PO Resp. 14, Figs. 1, 2; Ex. 1003, 2318; Ex. 1023, 3, Fig. 1. Patent Owner takes the position that abiraterone acetate "allows some cortisol to be made." Tr. 31:27–29. Although Patent Owner urges us to focus on the differences in the mechanisms of ketoconazole and abiraterone acetate, we look not only at the differences, but also at the similarities. The evidence demonstrates that one of ordinary skill would have been aware of the differences and the similarities in the mechanisms and, nevertheless, would have compared and analogized between the two. *See, e.g.*, Ex. 1003, 2318, Figure 1; Reply 6 (citing Ex. 1104 ¶¶ 14–31; Ex. 1097 ¶¶ 44–49). Both O'Donnell and Barrie refer to ketoconazole in their discussions of abiraterone acetate, indicating that teachings regarding ketoconazole administration were a starting point for exploration of abiraterone acetate administration. Ex. 1003, 2318; Ex. 1005, Table 1. O'Donnell, after evaluating ketoconazole as an agent, turns to an evaluation of abiraterone acetate as a more selective CYP17 inhibitor, i.e., as an improvement on ketoconazole. Ex. 1003, 2318. After presenting the

results from its studies, O'Donnell discusses that, in the clinical use of ketoconazole, "it is common practice to administer supplementary hydrocortisone" and that, therefore, "further studies with abiraterone acetate will be required to ascertain if concomitant therapy with glucocorticoid is required on a continuous basis, at times of physiological stress, if patients become symptomatic or indeed at all." *Id.* at 2323. This statement represents the proposition that one of ordinary skill in the art would use the example of ketoconazole's clinical use to take the next investigative steps with abiraterone acetate. We have not been presented with evidence that dissuades us from taking this statement at face value.

Thus, we are persuaded that one of ordinary skill in the art would understand that both ketoconazole and abiraterone are CYP17 inhibitors, albeit with different mechanisms. With this knowledge, and given the teachings of the prior art on administration of ketoconazole and administration of abiraterone acetate, we find that one of ordinary skill in the art would look to the administration of ketoconazole for guidance on how to administer abiraterone acetate.

b. Patent Owner's Second Argument

Patent Owner argues that O'Donnell establishes no need for glucocorticoid replacement with abiraterone acetate. PO Resp. 20. First, Patent Owner argues, O'Donnell reports no side effects of abiraterone acetate warranting glucocorticoid replacement. *Id.* (citing Ex. 2038 ¶¶ 109–16; Ex. 2040 ¶¶ 26, 30–35). According to Patent Owner, "based on the clinical evidence within O'Donnell itself, a skilled person would not have concluded that abiraterone acetate suppresses cortisol production to a degree that would necessitate concomitant glucocorticoid replacement therapy." *Id.* at 21.

Next, Patent Owner argues that O'Donnell's Synacthen test results did not establish a need for glucocorticoid replacement with abiraterone acetate. *Id.* at 24. Rather, Patent Owner argues, the Synacthen test results reported in O'Donnell "do not allow any meaningful conclusions to be drawn and would have been unhelpful in determining if a patient had a diagnosable adrenal disorder." *Id.* (citing Ex. 2040 ¶¶ 12–17, 27–29, 32–33; Ex. 2038 ¶¶ 115–18; Ex. 2051, 195; Ex. 2052, 927).

Petitioner replies that skilled artisans would have had concerns generally about the potential reduction in cortisol based on abiraterone acetate's inhibition of CYP17, and specifically, about adrenal insufficiency with abiraterone acetate. Reply 9–10. According to Petitioner, the prior art contained "independent data finding that abiraterone acetate may induce adrenal insufficiency." *Id.* at 10 (citing Ex. 1097 ¶¶ 48, 50–55, Ex. 1104 ¶¶ 40–48). Petitioner points to O'Donnell's Synacthen test and the abnormal test results by day 11, as well as O'Donnell's statement that "[s]ome impact on adrenal reserve was predictable from the steroid synthesis pathway," to support its argument that one of ordinary skill would have been motivated to administer glucocorticoid therapy with abiraterone acetate "to prevent potentially deadly adrenal insufficiency and low adrenal reserve." *Id.* at 10–11, 13.

We agree with Petitioner's plain reading of O'Donnell as indicating further investigation of the necessity of co-administration of a glucocorticoid with abiraterone acetate. O'Donnell clearly states that adrenocortical suppression may require administration of replacement glucocorticoid. Ex. 1003, Abstract, 2323. O'Donnell also states that "[s]ome impact on adrenal reserve was predictable from the steroid synthesis pathway." *Id.*

at 2323. Regarding administration of ketoconazole, O'Donnell states that "it is common practice to administer supplementary hydrocortisone" and that this may prove necessary with abiraterone acetate. *Id.* On the basis of the clinical evidence, O'Donnell reports that the need for concomitant therapy of abiraterone acetate with a glucocorticoid needs to be further investigated. *Id.* We disagree with Patent Owner that O'Donnell establishes that there is *no need* for glucocorticoid replacement with abiraterone acetate. Based on a plain reading, O'Donnell evaluates the evidence and expresses concerns based on the evidence regarding co-administration of a glucocorticoid with abiraterone acetate; it does not teach away from such co-administration, nor does it conclude that such co-administration is unnecessary.

Regarding the interpretation of O'Donnell's Synacthen test, we do not agree that the results "do not allow any meaningful conclusions to be drawn." PO Resp. 24. We are persuaded that one of ordinary skill in the art would understand the results of this test to be an indicator that something was amiss with the O'Donnell Study C patients' cortisol levels following administration of abiraterone acetate. Results of the Synacthen test led O'Donnell to conclude that further studies were needed to determine whether glucocorticoid replacement would be necessary. Ex. 1003, 2323. We understand Patent Owner's position that the "Synacthen test results in O'Donnell measure only cortisol, and do not account for the total glucocorticoid levels in the body" (PO Resp. 25), but do not perceive that a complete picture of a patient's glucocorticoid production is required for one of ordinary skill in the art to be motivated to explore whether glucocorticoid replacement therapy was necessary. Petitioner's experts opine that O'Donnell's Synacthen test was the standard diagnostic for adrenal

insufficiency and ideal for identifying early adrenal insufficiency. Reply 10–11 (citing Ex. 1097 ¶¶ 34–35, 48, 50; Ex. 1104 ¶¶ 40–48). Petitioner's experts also opine that low adrenal reserve, which is closely related to adrenal insufficiency and can be fatal, is likely when abnormal Synacthen results and otherwise normal cortisol levels and few symptoms are present. *Id.* at 11–12 (citing Ex. 1097 ¶¶ 38, 52–54, 71). We credit this testimony as supporting Petitioner's argument that one of ordinary skill in the art, upon reviewing O'Donnell's Synacthen test results and statement regarding impact on adrenal reserve, would not conclude that they lack any significance; rather, they would conclude that they are significant enough to merit further investigation of administration of abiraterone acetate with glucocorticoids.

c. Patent Owner's Third Argument

Patent Owner argues that ketoconazole with prednisone was not known to be "safe and effective" for prostate cancer in 2006. PO Resp. 27. First, Patent Owner argues, Gerber did not establish that ketoconazole with prednisone was safe and effective for prostate cancer. *Id.* (citing Ex. 2038 ¶¶ 167–87). Patent Owner disagrees that one of ordinary skill in the art would have read Gerber as Petitioner suggests, but rather, would have recognized that "Gerber advanced a scientifically unsupportable premise – that any decline in PSA in a treated patient was a 'response' to the combination treatment." *Id.* at 28. Second, Patent Owner argues that other prior art taught that ketoconazole with prednisone was not a safe and effective treatment of prostate cancer, but rather a "last resort" therapy for patients who had failed other options. *Id.* at 29. Patent Owner points to clinical test results showing that "ketoconazole in combination with a

glucocorticoid, such as hydrocortisone or prednisone, failed to provide any survival benefit in mCRPC in Phase II and Phase III studies." *Id.*

Petitioner replies that these arguments are "meritless" because, "even if true, *abiraterone acetate* was established as an effective prostate cancer treatment in 2006" and the claims recite abiraterone acetate, not ketoconazole. Reply 20–21. Petitioner also challenges Patent Owner's argument that ketoconazole and prednisone is not "safe and effective" because it is not FDA-approved. *Id.* at 21. Petitioner further argues that prior art use of glucocorticoids with steroid synthesis inhibitors is relevant because it would have suggested the combination to skilled artisans, pointing to ketoconazole's off-label prescription with prednisone or hydrocortisone to treat advanced prostate cancer. *Id.* (citing Ex. 1104 ¶¶ 16, 30, 34; Ex. 1003, 7; Ex. 1107).

We disagree that Petitioner's arguments and evidence regarding the administration of ketoconazole with prednisone are lacking. Gerber, despite the fact that it was not a Phase III trial, nevertheless is a peer-reviewed article published in a reputable journal, indicating that treatment with ketoconazole and prednisone demonstrated some degree of success in a group of patients. Ex. 1004. O'Donnell (2004), which is later in time than Gerber (1990), corroborates that in the clinical use of ketoconazole, it is "common practice" to administer supplementary hydrocortisone. Ex. 1003, 2323. Patent Owner's argument that ketoconazole was a "last resort" does not undercut the teachings of Gerber, or Gerber's demonstration that the combination of ketoconazole and prednisone worked for some patients, in which it was reasonably well tolerated, considering the circumstances. Ex. 1002 ¶¶ 33–35; Ex. 1004, 1079. Gerber reasonably stands for the proposition that

administration of ketoconazole and prednisone is tolerated and effective in a subset of patients, and at the time it was published, indicated some measure of efficacy for certain mCRPC patients. The prior art demonstrating use of ketoconazole with a glucocorticoid for advanced prostate cancer would have informed one of ordinary skill in the art that this was a possible approach to treatment.

d. Patent Owner's Fourth Argument

Patent Owner argues that prednisone's severe side effects would have dissuaded persons from using it without a clear clinical benefit. PO Resp. 30. First, Patent Owner argues, use of glucocorticoids was discouraged because of adverse side effects, particularly in prostate cancer patients. *Id.* Second, Patent Owner argues that the prior art taught that prednisone could fuel the prostate cancer. *Id.* at 32. Third, Patent Owner argues that, if symptoms of mineralocorticoid excess occurred, a skilled person would have addressed them with other available drugs, such as eplerenone, anti-hypertensives, diuretics, and potassium supplements. *Id.* at 35.

Petitioner replies that nothing about prednisone's side effects would have dissuaded skilled artisans from co-administering it with abiraterone acetate to advanced prostate cancer patients. Reply 19. First, Petitioner argues that prednisone's side effects were minimal and greatly outweighed by its prevention of potentially deadly side effects. *Id.* Second, Petitioner argues that the prior art did not teach that prednisone fueled prostate cancer. *Id.* at 20.

Although glucocorticoids have certain risks, we are not persuaded that those risks outweigh the positive effects in seriously ill patients with limited life expectancy, such that a person of ordinary skill in the art would have

been dissuaded from administering glucocorticoids to a mCRPC patient. We have sufficient evidence before us that the risks of glucocorticoid therapy were known, that the longevity of mCRPC patients was short, that glucocorticoid therapy was reasonably well tolerated in the short term, and that any long-term side effects would have been viewed by one of ordinary skill in the art in light of the same. Reply 19–20. Thus, we are persuaded that one of ordinary skill in the art would not have been dissuaded from administering abiraterone acetate with prednisone, but rather, would have been motivated to co-administer prednisone with abiraterone acetate.

Additionally, the existence of alternative treatments for mineralocorticoid excess, as discussed by Patent Owner, does not persuade us that one of ordinary skill in the art would employ these alternatives to the exclusion of prednisone. Rather, we are persuaded by Petitioner's argument that the better option for a typically high-risk, elderly population would have been co-administration of glucocorticoid replacement therapy. Reply 19 (citing Ex. 1104 ¶¶ 68–69; Ex. 1097 ¶ 97).

e. Patent Owner's Fifth Argument

Patent Owner argues that, in 2006, prednisone was not known to have anti-cancer effects. PO Resp. 35. More particularly, Patent Owner argues that a skilled person would not have considered prednisone to be an effective anti-cancer agent alone, and would have no expectation that co-administration of prednisone with abiraterone acetate would result in an enhanced anti-cancer effect. *Id.* at 35–36.

Petitioner replies that Patent Owner's position "merely compounds" Patent Owner's claim construction error. Reply 17. During the IPR2016-00286 proceeding, Petitioner notes, "the Board clearly held that 'treatment'

does not require an antitumor or anticancer effect." Reply 18 (citing IPR2016-00286, Decision on Institution (Paper 14) at 5; IPR2016-00286, Decision Denying Request for Rehearing (Paper 23) at 3 (rejecting Janssen's request for rehearing and noting that the Board's construction of "treating" does not require "having an anti-cancer effect on").

In making this argument, Patent Owner does not contest, but does discuss, our claim constructions of "therapeutically effective amount of prednisone," as well as "treat," "treating," and "treatment." PO Resp. 35–36. Our construction of "treat," "treating," and "treatment" comes directly from the specification: these terms "include the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer." We construed "therapeutically effective amount of prednisone" as "an amount of prednisone effective for treating prostate cancer," which invokes the term "treating."

The specification is directed to the administration of abiraterone acetate with "at least one additional therapeutic agent, *such an as anti-cancer agent or a steroid*." Ex. 1001, 1:10–12 (emphasis added). Therefore, the specification identifies, as therapeutic agents, both anti-cancer agents and steroids (the specification does not explicitly define "therapeutic agent").

The specification explicitly defines "anti-cancer agent" as "any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits, stops or reduces the proliferation of cancer cells." *Id.* at 4:8–16; *see also supra* (construing "anti-cancer agent"). The specification lists many examples of anti-cancer agents. *See, e.g.,* Ex. 1001, 3:17–18 (listing mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin,

seocalcitol, bicalutamide, and flutamide), 7:43–51 (listing hormone ablation agents, anti-androgen agents, differentiating agents, anti-neoplastic agents, kinase inhibitors, anti-metabolite agents, alkylating agents, *antibiotic agents,* immunological agents, interferon-type agents, intercalating agents, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, mitotic inhibitors, matrix metalloprotease inhibitors, genetic therapeutics, and anti-androgens) (emphasis added), 9:53–10:11. Thus, as set forth by the specification, antibiotic agents are one example of anti-cancer agents. *Id.* at 7:46. The specification lists examples of antibiotic agents, and includes in this list dexamethasone, corticosteroids such as hydrocortisone, *prednisone*, and prednisolone. *Id.* at 9:30–46. Therefore, prednisone, as an antibiotic agent, is an anti-cancer agent, according to the specification.

The specification does not explicitly define "steroid." The specification lists a few examples of steroids, namely, "corticosteroids or glucocorticoids" (*id.* at 10: 16–17), "hydrocortisone, *prednisone*, or dexamethasone" (*id.* at 3:19–20, 10:20–21 (emphasis added)), and "prednisolone" (*id.* at 10:35). In discussing administration of steroids, the specification provides that the "amount of the steroid administered to a mammal having cancer is an amount that is sufficient to *treat* the cancer whether administered *alone* or in combination with a 17α-hydroxylase/$C_{17, 20}$-lyase inhibitor." *Id.* at 10:21–24 (emphasis added).

The specification, therefore, appears to make a distinction between anti-cancer agents, on the one hand, and steroids, on the other hand. They are treated in the specification as two different categories of therapeutic agents. *See id.* at 3:15–20 ("a therapeutically effective amount of at least one

additional anti-cancer agent, such as, but not limited to, mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, flutamide, or a steroid including, but not limited to, hydrocortisone, prednisone, or dexamethasone.").

The anti-cancer agent exemplars in the specification have an anti-cancer effect, as that term is defined. The four steroid examples given (dexamethasone, hydrocortisone, prednisone, and prednisolone), which are identified as antibiotic agents and therefore anti-cancer agents, presumably have an anti-cancer effect. However, because steroids are discussed separately from anti-cancer agents in the specification, they are treated differently than anti-cancer agents: the identified steroids are anti-cancer agents, but they also are treated by the specification as a different category of therapeutic agents. Although steroids may have anti-cancer effects, as suggested by the evidence we have before us in the specification, the specification does not foreclose that they may also have other therapeutic effects. It would make little sense for the specification to identify the four steroid examples given as anti-cancer agents, and then to address them again as steroids, if these four steroid examples did not have an effect apart from an anti-cancer effect.

Treatment, according to the '438 specification, therefore, can include eradication of a tumor, as would be expected of an anti-cancer agent. Treatment, however, need not exclude other effects that may be provided by steroids. Treatment by steroids can also refer to the other treatments that are "included" in the construction of "treat," "treating," and "treatment," such as management or control of a tumor, cancer cells or tissue, and minimization or delay of the spread of cancer. "As a patent law term of art, 'includes' means

'comprising.'" *SanDisk Corp. v. Memorex Products, Inc.*, 415 F.3d 1278, 1284 (Fed. Cir. 2005) (citations omitted). The terms "management" and "control" in the definition also do not foreclose that the terms "treat," "treatment," or "treating" may refer to different effects derived from administration of steroids, apart from anti-cancer effects, such as palliative effects.

We construed "therapeutically effective amount of prednisone" as "an amount of prednisone effective for treating prostate cancer." Thus, because "treating" can "include" a number of actions, prednisone may be used to "treat" prostate cancer, perhaps by an anti-cancer effect, or perhaps by some other mechanism. Thus, we determine that Petitioner has met its burden that the prior art provides a reasonable expectation that prednisone could be used as a therapeutic agent in the treatment of prostate cancer.

f. Patent Owner's Sixth Argument

Patent Owner argues that a skilled person would not have had a reasonable expectation of success in achieving the '438 patented invention. PO Resp. 37. More particularly, Patent Owner argues that the prior art provided no basis for a skilled person to expect prednisone would provide anti-prostate cancer effects. *Id.* Additionally, Patent Owner argues that the unpredictability of drug combination therapy for prostate cancer precludes obviousness. *Id.* at 40.

Because this argument is premised on the same claim construction principles as Patent Owner's fifth argument, we refer to and incorporate our analysis regarding the same, *supra*, to address this argument. Regarding Patent Owner's unpredictability argument, we note that Claim 1, which is directed to the administration of abiraterone acetate and prednisone, does not

require a particular result. It does require a "therapeutically effective amount" of each component, but as we have discussed above, the claim language does not require any unexpectedly synergistic anti-cancer results. Moreover, although ketoconazole and prednisone do not meet Patent Owner's measure of "success," Gerber and other art nevertheless disclose its effective administration to a subset of patients. Therefore, Patent Owner's unpredictability argument, viewed in light of the language of the challenged claims and the evidence of record, does not convince us that the Petitioner has not established by a preponderance of the evidence a reasonable expectation of achieving the method for treatment of a prostate cancer in a human recited by the challenged claims.

g. Patent Owner's Seventh Argument

Patent Owner argues that Petitioner's obviousness grounds rely on hindsight. PO Resp. 41. More particularly, Patent Owner argues that Petitioner ignores the "unpredictable landscape facing the skilled person in 2006 and instead frames the questions as whether there is any conceivable reason for using prednisone with abiraterone acetate in the treatment of prostate cancer." *Id.* at 42.

Petitioner challenges this argument, asserting that despite Patent Owner's allegations of "hindsight bias," Patent Owner "never disputes that abiraterone acetate was known to be effective for treating prostate cancer, in part based on past successes with ketoconazole and aminoglutethimide." Reply 6 n.2.

We are unpersuaded, based on the evidence before us on the full record, that Petitioner's reasoning demonstrates impermissible hindsight. *See, e.g., In re McLaughlin,* 443 F.2d 1392, 1395 (CCPA 1971) ("Any

judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper."). Although the thrust of the research in the relevant area at the relevant time may have focused on different approaches to prostate cancer, the art cited by Petitioner discloses that some research focused on use of a CYP17 inhibitor with glucocorticoids to treat prostate cancer. This persuades us that Petitioner's reasoning incorporates and relies on the knowledge of those of ordinary skill in the art at the time of the invention, notwithstanding Patent Owner's arguments that this research was overshadowed by a different line of investigation.

h. Patent Owner's Eighth Argument

Patent Owner argues that Petitioner has failed to meet its burden of demonstrating obviousness of the claimed invention, pointing particularly to its arguments regarding motivation to combine. PO Resp. 43. Patent Owner argues that (1) O'Donnell and Gerber do not provide a reason to use prednisone with abiraterone acetate to treat prostate cancer; (2) Barrie and Gerber do not provide a reason to use prednisone with abiraterone acetate to treat prostate cancer; and (3) the prior art taught away from using prednisone in prostate cancer patients. *Id.* at 43–47. Regarding the combination of O'Donnell and Gerber, Patent Owner argues that they provide no "safety and tolerability" reasons to administer prednisone with abiraterone acetate, and that a person of ordinary skill would have been dissuaded from administering prednisone to a prostate cancer patient without a demonstrated clinical need. *Id.* at 45. Regarding Barrie and Gerber, Patent Owner argues that Barrie

"says nothing about glucocorticoid replacement or prednisone with any of the many compounds disclosed" and, thus, the combination provides no logical reason for a skilled person to treat a prostate cancer patient with prednisone and abiraterone acetate. *Id.* at 46. Regarding teaching away, Patent Owner argues that the prior art demonstrates that "a skilled person would have found substantial reasons not to co-administer prednisone with abiraterone acetate to treat prostate cancer patients." *Id.* at 47.

In both its grounds, Petitioner states that the motivation to add prednisone to the method of treating prostate cancer of either O'Donnell or Barrie is seen in Gerber, which teaches that the administration of ketoconazole, a CYP17 inhibitor, in combination with 5 mg prednisone twice daily, is safe and effective in treating human patients with hormone-refractory prostate cancer. Pet. 40–41. Thus, the absence of mention of glucocorticoid replacement or prednisone in Barrie does not change the analysis of whether Gerber provides motivation to combine. For the first ground based on O'Donnell, Petitioner further states that "concomitant hormone replacement therapy with a glucocorticoid may be needed when using abiraterone acetate to treat prostate cancer in a human patient." *Id.* at 39. Regarding O'Donnell, we are persuaded, as we have discussed above, that one of ordinary skill in the art would have translated the clinical experience with ketoconazole to abiraterone acetate.

The teachings of the references do not rise to the level of teaching away from Petitioner's proposed combination—they do not criticize, discredit, or otherwise discourage the solution claimed. *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) (explaining "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away

from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed"). Rather, as Petitioner argues, the prior art encourages exploration of such a combination. Pet. 38–42. Thus, we find that the prior art does not teach away from administration of prednisone to mCRPC patients.

3. Objective Indicia of Non-Obviousness

In its Petition, Petitioner contends that the Patent Owner may try to rely on secondary considerations of non-obviousness. Pet. 51–61. Specifically, the Petition raises arguments related to commercial success, unexpected results, long-felt need, the existence of a blocking patent, and copying. *Id.*

In its Response, Patent Owner presents arguments directed to objective indicia of nonobviousness. PO Resp. 48–64. Patent Owner argues that the objective indicia of non-obviousness demonstrate: 1) unexpected results; 2) skepticism and the failure of others; 3) the claimed invention has met a long-felt need; and 4) the claimed invention has significant commercial success. *Id.*

In its Reply, Petitioner presents arguments related to unexpected results, skepticism and failure of others, long-felt but unmet need, and commercial success. Reply 22–27.

Factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham*, 383 U.S. at 17. Secondary considerations may include any of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *Id.* The totality of the evidence submitted may show that the challenged claims

would not have been obvious to one of ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Before we make our final obviousness determination, we must consider the evidence of obviousness anew in light of any evidence of secondary considerations of nonobviousness presented by Patent Owner. *See Graham*, 383 U.S. at 17–18 ("Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy."); *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) ("This objective evidence must be 'considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.'" (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983))).

All types of objective evidence of nonobviousness must be shown to have a nexus to the claimed invention. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) (nexus generally); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (commercial success); *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (unexpected results); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (long-felt need). The stronger the showing of nexus, the greater the weight accorded the objective evidence of nonobviousness. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985).

a. Unexpected Results

Patent Owner asserts that unexpected results are demonstrated by groundbreaking clinical studies showing that the addition of a glucocorticoid

unexpectedly enhanced the response to abiraterone acetate. PO Resp. 48. According to Patent Owner, a first clinical study involved abiraterone acetate monotherapy and an "extension study" in which dexamethasone was co-administered to patients. *Id.* (citing Ex. 2014, Abstract; Ex. 2133). In this study, "when a glucocorticoid was added to the treatment regimen after a patient stopped responding to abiraterone acetate monotherapy, many patients started responding again, regardless of whether that patient's disease had worsened while on glucocorticoids in the past." *Id.* at 49–50. Patent Owner presents a table comparing abiraterone acetate monotherapy to abiraterone acetate administered with dexamethasone (in clinical trial COU-AA-001, from Ex. 2015) and to abiraterone acetate administered with prednisone (in clinical trial COU-AA-002, from Ex. 2017) to argue that patients given abiraterone acetate with prednisone responded for more than twice as long on average as those given abiraterone acetate alone. *Id.* at 53–54. Patent Owner concludes that the "combination therapy provided patients with advanced prostate cancer an overall survival benefit, which is exceedingly uncommon in prostate cancer drug development." *Id.* at 54.

In the Petition, Petitioner argues that the prednisone administered in the approved indication for Zytiga (the trademark for abiraterone acetate) is intended as hormone replacement therapy, not as an anti-cancer therapy, and therefore, one of ordinary skill in the art would not expect the combination of prednisone and abiraterone acetate to yield "any additional clinically significant anti-cancer benefit." Pet. 54–55. To the extent that co-administration of prednisone with abiraterone acetate "made treatment of prostate cancer with abiraterone safer and/or more tolerable, this greater safety and/or tolerability was expected." *Id.* at 58. In the Reply, Petitioner

argues that the Response (1) did not show a statistically significant difference between any of the time to PSA progression ("TTPP") estimates it compared; (2) omitted contradictory data from its other clinical trials; (3) ignores that the patients in the study producing longer TTPP were healthier at the start of the study; and (4) has not shown that the claimed combination produces any survival advantage over abiraterone acetate alone, which could be attributed to the use of prednisone. Reply 22–23. Petitioner further argues that the challenged claims do not claim treating patients with abiraterone acetate and dexamethasone, but rather, treating patients with abiraterone acetate and prednisone. *Id.* at 23–24.

Regarding Patent Owner's comparison of abiraterone acetate monotherapy with abiraterone acetate/dexamethasone therapy, we agree with Petitioner that this evidence "tells you something about the combination of abiraterone with dexamethasone. It tells you nothing about the combination we have here, abiraterone plus prednisone." Tr. 18:8–10. Although dexamethasone and prednisone are both glucocorticoids, Petitioner points to evidence indicating that dexamethasone and prednisone had different activities. Tr. 38:13–16 (citing Ex. 1104 ¶¶ 104–06). Because the claims cover prednisone, and not any other glucocorticoid, the results of the combination of dexamethasone with abiraterone acetate are of limited use, as we are not informed of the similarities or differences of the mechanism of action of those glucocorticoids or how the mechanism leads to the asserted unexpected results.

Moreover, to the extent the table purportedly compares the abiraterone acetate monotherapy to abiraterone acetate administered with prednisone, the table compares the abiraterone acetate monotherapy administered in clinical

trial COU-AA-001 with the abiraterone acetate administered with prednisone in clinical trial COU-AA-002, without explaining or accounting for the differences between the two trials. PO Resp. 51–54.

We determine that there is insufficient evidence that the alleged unpredictable and unexpected results of abiraterone acetate and prednisone are objective indicia of nonobviousness of the challenged claims. Patent Owner does not sufficiently tie the allegedly unpredictable and unexpected result to the administration of abiraterone acetate and prednisone as claimed. Thus, we determine this consideration does not weigh in favor of the patentability of the challenged claims.

b. Skepticism and the Failure of Others

Patent Owner describes the history of abiraterone acetate development as a series of starts and stops. PO Resp. 55–57. The sponsor of the research described in O'Donnell, according to Patent Owner, lost interest and terminated the development program in 1999. *Id.* No clinical data concerning abiraterone acetate was published until O'Donnell in 2004. *Id.* at 54. During this time, other potential therapeutic agents and regimens for prostate cancer were investigated without success. *Id.* at 56–57.

Petitioner argues that the testimony of Patent Owner's declarant, Dr. Judson, refutes Patent Owner's arguments. *See* Reply 24–25. Petitioner also argues that Patent Owner's failure of others evidence is irrelevant as it is not directed to others' attempts to improve abiraterone acetate's side effects, or even to abiraterone acetate at all. *Id.* at 25.

"Evidence of industry skepticism weighs in favor of non-obviousness. If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it

favors non-obviousness." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016).

Based on Patent Owner's evidence, it does appear that abiraterone acetate was viewed with some skepticism until the application for the '438 patent was filed in 2006. However, abiraterone acetate was also previously patented in 1997 (Barrie), and therefore at least some in the industry had overcome their skepticism sufficiently to undertake research on and to seek a patent on the invention of abiraterone acetate alone. Moreover, the claims at issue are directed to the combination of abiraterone acetate with prednisone, whereas Patent Owner's arguments are directed to the purported skepticism of the industry toward abiraterone acetate alone, which falls short of establishing a nexus between skepticism of the industry and the challenged claims. Finally, the "failure of others" argument as it relates to the combination of abiraterone acetate with prednisone may have come about as a result of other factors, such as a blocking patent (Barrie), as we discuss more fully below. Thus, we determine that these factors do not weigh in favor of patentability of the challenged claims.

c. Long-Felt Need

According to Patent Owner, before to the invention claimed in the '438 patent, "the prognosis for men with mCRPC was dismal," and thus, "there was an urgent need for new agents that would improve survival." PO Resp. 57.

In the Petition, Petitioner argues that "any success of Zytiga® that is not a result of the alleged novel features of the claimed invention is irrelevant to secondary considerations" because the combination of abiraterone acetate and prednisone does not produce unexpected results in anti-cancer benefit,

and "the perception among clinicians is that the requirement to coadminister prednisone with Zytiga is a drawback to its use to treat prostate cancer." Pet. 59 (citing Ex. 1017 ¶¶ 23, 29–34; Ex. 1002 ¶¶ 84, 90, 93–96). Petitioner also argues that any need for a clinically efficacious treatment was satisfied by abiraterone acetate itself, or by Xtandi, a competing drug claimed in patents filed more than a year before the earliest priority date of the '438 patent. Reply 25.

We determine that, although drugs that contribute to increasing cancer patient survival rates nearly always satisfy a long-felt need, Patent Owner has not presented sufficient evidence that a specific long-felt need existed for the method of administering abiraterone acetate and prednisone claimed in the '438 patent. Abiraterone acetate's availability (and underutilization) for approximately a decade prior to issuance of the '438 patent undermines Patent Owner's argument that a long-felt need existed for any regimen based on abiraterone acetate. The record also indicates that, although there were drawbacks to the existing drugs, there were other drugs on the market that were available to prostate cancer patients. Ex. 1002 ¶¶ 96; Ex. 1104 ¶¶ 112–13. We are not satisfied that long-felt need is necessarily objective indicia of nonobviousness of the challenged claims. Thus, we determine this consideration is neutral regarding the patentability of the challenged claims.

d. Commercial Success

Patent Owner argues that "ZYTIGA® therapy has been an outstanding commercial success, with U.S. sales reaching $1.07 billion in 2015 and $1.09 billion in 2016." PO Resp. 58. Patent Owner criticizes Mr. Hoffman's analysis of Zytiga's market share, arguing that under any metric, Zytiga has achieved substantial market share. *Id.* at 60–61. To support its argument,

Patent Owner presents evidence of market share. *Id*. at 59–61 (citing Ex. 1012, 6–8; Ex. 2044 ¶¶ 8–9, 64–68, Appendix C, C-1, D). Patent Owner also presents evidence that there is a nexus between the '438 patent claims and the commercial success of Zytiga. *Id.* at 61 (citing Ex. 2038 ¶¶ 214–19; Ex. 2044 ¶¶ 54–61).

In its Petition, discussing the prosecution history, Petitioner argues that the information presented to the Examiner "fails to show any nexus between the claimed combination and the commercial performance of Zytiga." Pet. 52–53. Petitioner also argues that applicants made no effort during prosecution to suggest that the claimed invention, rather than the prior art abiraterone acetate, was responsible for the commercial success of Zytiga. *Id.* at 53. More particularly, Petitioner argues that Zytiga is a commercial embodiment of Barrie, rather than the '438 patent. *Id.* at 53–54. Petitioner further argues that the existence of a blocking patent (here, Barrie) limits the applicability of any evidence of commercial success to overcome a prima facie case of obviousness. *Id.* at 59–60 (citing *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376–77 (Fed. Cir. 2005)). In its Reply, Petitioner reiterates (1) the significance of the Barrie patent as a blocking patent; (2) that Petitioner fails to establish any nexus to the '438 claims; and (3) that the commercial success evidence submitted to the examiner was insufficient to demonstrate commercial success. Reply 25–27. Petitioner does not materially dispute the $1.07 billion or $1.09 billion annually in sales figures.

"When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *J.T. Eaton & Co. v.*

Atl. Paste & Glue Co., 106 F.3d 1563, 1571 (Fed. Cir. 1997); *WBIP*, 829 F.3d at 1329. That presumption of nexus, however, is rebuttable, as "a patent challenger may respond by presenting evidence that shows the proffered objective evidence was 'due to extraneous factors other than the patented invention.'" *WBIP*, 829 F.3d at 1329 (quoting *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1393 (Fed. Cir. 1988)).

There is no real dispute that Zytiga is commercially successful in terms of dollar figures. PO Resp. 58. However, as discussed herein, abiraterone acetate was previously known and patented. Ex. 1005. "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) (quoting *Merck & Co.*, 395 F.3d at 1377). Even if the Barrie patent were "available for licensing and was actively shopped around to other companies" between 2000 (after which a previous license expired) and 2004 (when the predecessor of Patent Owner took a license), the record evidence does not indicate that those efforts in this span of time remove the deterrent effect of the blocking patent. PO Resp. 63 (citing Ex. 2044 ¶¶ 26, 29–33); Reply 25 (citing Ex. 1134 ¶¶ 8–17). Thus, although the revenues generated by Zytiga are substantial, the commercial success of Zytiga is mitigated by the existence of a blocking patent. We are persuaded, rather, by Petitioner's argument that the blocking patent would have deterred others from exploring the commercial potential of abiraterone acetate, and thus, that blocking patent to abiraterone acetate limits the applicability of other evidence of commercial success.

We also note Petitioner's argument that there is no nexus between the commercial success and the claimed invention, in that the record evidence attributes Zytiga's commercial success to abiraterone acetate, rather than to the combination of abiraterone acetate and prednisone. Reply 21–23. In this case, if the feature that created the commercial success was known in the prior art, i.e., abiraterone acetate, the success is not pertinent to the issue of obviousness. *Galderma Labs.*, 737 F.3d at 740. As the Zytiga prescribing information indicates, the stated purpose of co-administration of prednisone or "a corticosteroid" is reducing the incidence of adverse reactions due to CYP17 inhibition. Ex. 1018, 3–6 ("[c]o-administration of a corticosteroid" suppresses ACTH drive, resulting in a reduction in the incidence and severity of adverse reactions such as hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition); Ex. 1019, 2–3 (co-administration of a corticosteroid suppresses the ACTH drive, reducing the incidence and severity of mineralocorticoid adverse reactions). Also, this literature's discussion of a corticosteroid generally contradicts the specific anti-cancer role of prednisone argued by Patent Owner. As discussed in the prescribing literature, and as supported by Petitioner's expert testimony here, Zytiga's anti-cancer effects come from abiraterone acetate. Ex. 1002 ¶¶ 81–82, 85–88. We are unpersuaded that there is a nexus between the commercial method, namely, the administration of abiraterone acetate and prednisone, and any novel features of the claimed method. Petitioner has demonstrated that both abiraterone acetate and prednisone were known in the prior art. Patent Owner's assertions that the combination of these features drove Patent Owner's increased sales do not

demonstrate a nexus between any commercial success and the claimed invention of the '438 patent.

Thus, on this record, it is not clear whether the sales of Zytiga are due to the method recited in the '438 patent, or the known and patented abiraterone acetate itself. Consequently, we cannot conclude from the evidence before us that the commercial success of Zytiga was due to the merits of the invention recited in the claims of the '438 patent. Accordingly, we determine that Petitioner presents sufficient evidence to rebut the presumption of nexus between the commercial success of Zytiga and the claimed method. We, therefore, are not persuaded that Patent Owner's evidence of commercial success supports the nonobviousness of the challenged claims.

4. Summary

As detailed above, the secondary considerations of nonobviousness raised by Patent Owner are neutral or not in favor of the patentability of the challenged claims, and do not outweigh the other *Graham* factors in our obviousness analysis. We determine, therefore, that Petitioner has demonstrated that the preponderance of the evidence of record supports that it would have been obvious to the ordinary artisan at the time of invention to combine Gerber with either O'Donnell or Barrie, with a reasonable expectation of success of achieving the method of challenged claim 1. We also have considered Petitioner's arguments and evidence as to dependent claims 2–20, which reasoning we adopt as our own. We are persuaded, based on those arguments, that Petitioner has demonstrated by a preponderance of the evidence that those claims would have been obvious based on the

combination of Gerber and O'Donnell (for claims 2–20) and Gerber and Barrie (for claims 2–4 and 6–11). *See* Pet. 42–50; Ex. 1002 ¶¶ 60–76.

F. Patent Owner's Motion to Exclude

Patent Owner filed a Motion to Exclude (Paper 69), to which Petitioner responded (Paper 76) and to which Patent Owner filed a Reply (Paper 80). The party moving to exclude evidence bears the burden of proof to establish that it is entitled to the relief requested, e.g., that the material sought to be excluded is inadmissible under the Federal Rules of Evidence. *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

Patent Owner seeks to exclude Exhibits 1002 ¶ 30; 1017; 1017 [B-1]; 1028; 1040; 1041; 1046–51; 1053–55; 1057; 1064–66; 1088; 1089; 1091 ¶¶ 17–29, 31; 1092–95; 1097, ¶¶ 11–16, 95; 1100, 1102, 1103; 1104 ¶¶ 5–9, 11–13, 88–90, 92–95, and 119–22; 1117; 1125; and 1139. Paper 69, 10. Patent Owner seeks to exclude these exhibits as (a) expert declarations and exhibits that Patent Owner alleges are outside of the scope of the prior art permitted by 35 U.S.C. § 311(b); (b) sections of Petitioner's declarations that are not cited in the briefs, and therefore irrelevant and prejudicial; and (c) exhibits that lack authenticity or violate the hearsay rule. *Id.* at 1.

Petitioner responds that (a) the Board should consider all of Petitioner's commercial success evidence; (b) the Board should consider the full record of submitted evidence, all of which is relevant and supports Petitioner's obviousness positions; and (c) the Board should consider the exhibits objected to due to lack of authenticity and hearsay, arguing that Exhibits 1017 [B-1], 1028, 1048, 1049, 1053, 1055, 1057, 1088, 1092, 1095, 1117, and 1125 have been properly authenticated by timely served

supplemental evidence, and that Exhibits 1055, 1088, and 1095 are not inadmissible hearsay. Paper 76, 1–13.

Because we do not expressly rely upon Exhibits 1017 [B-1]; 1028; 1040; 1041; 1046–51; 1053–55; 1057; 1064–66; 1086; 1088; 1089; 1092–95; 1100, 1102, 1103; 1117, 1125; and 1139 in this Decision, Patent Owner's Motion to Exclude need not be decided as to these exhibits. Accordingly, Patent Owner's Motion to Exclude is dismissed as moot as to these Exhibits. Below, we address concerns regarding Exhibits 1002, 1017, 1091, 1097, and 1104.

We do not construe Petitioner's preliminary arguments concerning secondary considerations to be a ground on which this proceeding is based. 35 U.S.C. § 311(b). We credit Petitioner's argument that the evidence Patent Owner seeks to exclude is relevant to evaluating whether the Examiner erred in allowing the '438 patent and whether Patent Owner can establish commercial success in this proceeding. Paper 76, 5. We therefore find that Exhibit 1017 concerning secondary considerations is properly part of the record.

Regarding the portions of declarations and exhibits that were not specifically cited in Petitioner's papers, we disagree with Patent Owner that we should exclude these portions. In our proceedings, "[e]vidence consists of affidavits, transcripts of depositions, documents, and things. All evidence must be filed in the form of an exhibit." 37 C.F.R. § 42.63(a). An exhibit "must be filed with the first document in which it is cited." 37 C.F.R. § 42.6(c). The Petition, as filed, references Exhibit 1002 in its List of Exhibits. Pet. vi. Exhibit 1002 was filed along with the Petition. The Reply, as filed, references Exhibits 1091, 1097, and 1104 in its List of Exhibits.

Paper 56, 8–9. Exhibits 1091, 1097, and 1104 were filed along with the Reply. We find the references to these documents adequate to support the "cited" requirement in 37 C.F.R. § 42.6(c). We are unaware of any legal basis for striking uncited paragraphs of an expert declaration or unrelied-upon portions of an exhibit. Thus, the portions of Exhibits 1002, 1091, 1097, and 1104 sought to be excluded are not inadmissible, and we shall not exclude them as such.

Accordingly, Patent Owner's Motion to Exclude is *denied* as to Exhibits 1002, 1017, 1091, 1097, and 1104, and *dismissed* as to Exhibits 1017 [B-1]; 1028; 1040; 1041; 1046–51; 1053–55; 1057; 1064–66; 1086; 1088; 1089; 1092–95; 1100; 1102; 1103; 1117; 1125; and 1139.

G. Petitioner's Motion to Exclude

Petitioner filed a Motion to Exclude (Paper 72), to which Patent Owner responded (Paper 78) and to which Petitioner filed a Reply (Paper 81). The party moving to exclude evidence bears the burden of proof to establish that it is entitled to the relief requested, e.g., that the material sought to be excluded is inadmissible under the Federal Rules of Evidence. *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

Petitioner seeks to exclude (a) Exhibits 2010, 2037, 2120, 2122, 2124, 2125, and 2127 as embodying testimony prepared specifically for IPR2016-00286; (b) Exhibit 2151 as embodying Patent Owner's Response in IPR2016-00286; (c) Exhibit 2134 as unauthenticated, hearsay, and incomplete; and (d) Ex. 2118 as hearsay. Paper 72, 1–13.

Because we do not expressly rely upon any of these exhibits in this Decision, Petitioner's Motion to Exclude need not be decided as to these exhibits. Accordingly, Petitioner's Motion to Exclude is *dismissed* as moot

as to Exhibits 2010, 2037, 2120, 2122, 2124, 2125, 2127, 2151, 2134, and 2118.

H. Motions to Seal

Patent Owner filed a Motion to Seal (Paper 34), moving to seal the confidential version of the Declaration of Dr. Vellturo (Exhibit 2044) as well as Exhibits 2092, 2093, and 2118. Patent Owner represents that the parties agreed to a modified version of the Board's Default Protective Order, submitted as Exhibit 2113, and submitted a redline of the Standing Protective Order as Exhibit 2114. Paper 34, 1.

Petitioner filed a Motion to Seal (Paper 57), moving to seal the confidential version of the Declaration of Dr. Auchus (Exhibit 1143) and the confidential version of the Declaration of Dr. Hoffman (Exhibit 1134).

The motions to seal are *granted* and the modified protective order *entered*.

There is an expectation that information will be made public where the information is identified in a final written decision, and that confidential information that is subject to a protective order ordinarily would become public 45 days after final judgment in a trial, unless a motion to expunge is granted. 37 C.F.R. § 42.56; Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,761 (Aug. 14, 2012). In rendering this Final Written Decision, it was not necessary to identify, nor discuss in detail, any confidential information. However, a party who is dissatisfied with this Final Written Decision may appeal the Decision pursuant to 35 U.S.C. § 141(c), and has 63 days after the date of this Decision to file a notice of appeal. 37 C.F.R. § 90.3(a). Thus, it remains necessary to maintain the record, as is, until resolution of an appeal, if any.

In view of the foregoing, the confidential documents filed in the instant proceeding will remain under seal, at least until the time period for filing a notice of appeal has expired or, if an appeal is taken, the appeal process has concluded. The record for the instant proceeding will be preserved in its entirety, and the confidential documents will not be expunged or made public, pending appeal. Notwithstanding 37 C.F.R. § 42.56 and the Office Patent Trial Practice Guide, neither a motion to expunge confidential documents nor a motion to maintain these documents under seal is necessary or authorized at this time. *See* 37 C.F.R. § 42.5(b).

I. Conclusion

Having considered the parties' arguments and evidence, we evaluate all of the evidence together to make a final determination of obviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012) (stating that a fact finder must consider all evidence relating to obviousness before finding patent claims invalid). In so doing, we conclude that Petitioner has satisfied its burden of demonstrating, by a preponderance of the evidence, that the subject matter of claims 1–20 would have been obvious over the combination of Gerber and O'Donnell and that claims 1–4 and 6–11 would have been obvious over the combination of Gerber and Barrie.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–20 are held *unpatentable*;

FURTHER ORDERED that Patent Owner's Motion to Exclude is *denied* as to Exhibits 1002, 1017, 1091, 1097, and 1104 and *dismissed* as to

Exhibits 1017 [B-1]; 1028; 1040; 1041; 1046–51; 1053–55; 1057; 1064–66; 1086; 1088; 1089; 1092–95; 1100; 1102; 1103; 1117; 1125; and 1139;

FURTHER ORDERED that Petitioner's Motion to Exclude is *dismissed* as moot;

FURTHER ORDERED that the parties' Motions to Seal are *granted* and the modified protective order *entered*; and

FURTHER ORDERED, because 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.

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