

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMERIGEN PHARMACEUTICALS LIMITED and
ARGENTUM PHARMACEUTICALS LLC,
Petitioner,

v.

JANSSEN ONCOLOGY, INC.,
Patent Owner.

Case IPR2016-00286¹
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

¹ Case IPR2016-01317 has been joined with this proceeding.

I. INTRODUCTION

Amerigen Pharmaceuticals Limited (“Amerigen”) 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 12, “Prelim. Resp.”). We instituted an *inter partes* review of claims 1–20 on certain grounds of unpatentability alleged in the Petition (Paper 14, “Dec.”).

Argentum Pharmaceuticals LLC (“Argentum”) filed a Petition for *inter partes* review of claims 1–20 of the ’438 patent. Case IPR2016-01317, Paper 2. Together with its Petition, Argentum filed a Motion for Joinder to join the case with the previously instituted proceeding in IPR2016-00286. *Id.*, Paper 3. We instituted trial in IPR2016-01317 and joined Argentum as a Petitioner in IPR2016-00286. *Id.*, Paper 9.

After institution of trial, Patent Owner filed a Patent Owner Response (Paper 33, “PO Resp.”). Amerigen and Argentum (collectively, “Petitioner”) filed a Reply (Paper 60, “Reply”). Pursuant to a Board Order (Paper 68), Patent Owner filed an Identification of New Arguments and Evidence in Petitioner’s Reply (Paper 74), to which Petitioner filed a Reply (Paper 78). An oral hearing was held on February 16, 2017. A transcript of the hearing has been entered into the record. Paper 85 (“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 6, 2–3. 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.), *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-03743-KM-JBC (D.N.J.). Paper 57, 2–3.

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 18, 2.

B. The '438 Patent

The '438 patent, titled “Methods and Compositions for Treating Cancer,” describes methods that comprise “administering a 17 α -hydroxylase/C_{17,20}-lyase inhibitor, such as abiraterone acetate (i.e., 3 β -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 17 α -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 17 α -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 Scott R. Serels, M.D. (Ex. 1002; Ex. 1095), DeForest McDuff, Ph.D. (Ex. 1017; Ex. 1096), Mark J. Ratain, M.D. (Ex. 1091), and Richard Dorin, M.D. (Ex. 1093). Patent Owner relies on the declarations of Matthew Rettig, M.D. (Ex. 2038), Richard Auchus, M.D., Ph.D. (Ex. 2040), Gerald Walter Chodak, M.D. (Ex. 2042), and Christopher A. Vellturo, Ph.D. (Ex. 2044).

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. Those claim terms are discussed and defined explicitly in the specification of the ’438 patent, as noted by Petitioner. *Id.* at 18; Ex. 1001, 3:31–5:5. In our Decision on Institution, 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

Patent Owner, in its Response, states that our Decision on Institution properly construed “a therapeutically effective amount of prednisone” and the terms “treat,” “treating,” and “treatment.” PO Resp. 8.

Patent Owner also submitted a claim construction of the terms “treatment” and “treating” by the district court in a companion litigation. Ex. 2122. 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. § 103² 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

² 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.

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 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 or oncology, or holding a Ph.D. in pharmacology, biochemistry or a related discipline. 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 enzymologist and/or molecular biologist 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 17 α -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.” Pet. 6 (citing Ex. 1002 ¶¶ 32, 34, 48). Cortisol is “necessary for other biochemical cycles in the body and its reduced production caused adverse effects, including hypertension, hypokalemia (decrease in circulating potassium levels), and fluid retention.” *Id.* 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.* (citing Ex. 1002 ¶ 31). 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 ¶ 32).

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. 36–48.

Regarding claim 1, Petitioner argues that O'Donnell teaches “that abiraterone acetate is a selective CYP17 inhibitor that is more effective in

suppressing testosterone levels in a mammal *in vivo* than ketoconazole, a CYP17 inhibitor known in the art.” Pet. 37 (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 teaches that concomitant hormone replacement therapy with a glucocorticoid may be needed for continuous use of abiraterone acetate in treating a prostate cancer in a human patient.” *Id.* at 38 (citing Ex. 1003, Abstract, 2323). Gerber, Petitioner argues, teaches that “the combination of ketoconazole and prednisone is safe and effective in treating human patients with hormone-refractory advanced prostate cancer.” *Id.* at 38–39 (citing Ex. 1004, Abstract, 1177–79).

Regarding motivation to combine, Petitioner reasons that the “motivation to add prednisone to a method of treating prostate cancer in a human patient that includes abiraterone acetate is clearly 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.” *Id.* at 38. One of ordinary skill in the art, Petitioner argues, would have combined abiraterone acetate and prednisone “with a reasonable expectation of success because the prior art taught abiraterone acetate as a more effective CYP17 inhibitor than ketoconazole and the combination of ketoconazole and prednisone as safe and effective to treat patients with hormone refractory metastatic prostate cancer.” *Id.* at 7 (citing Ex. 1002 ¶¶ 45–49).

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. *Id.* at 40–48.

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. 36–45.

Regarding claim 1, Petitioner argues that Barrie teaches “that abiraterone acetate is a selective CYP17 inhibitor that is more effective in suppressing testosterone levels in a mammal in vivo than ketoconazole, a CYP17 inhibitor known in the art.” Pet. 37, 39 (citing Ex. 1005, 25:13–26:63). Gerber, Petitioner argues, teaches that “the combination of ketoconazole and prednisone is safe and effective in treating human patients with hormone-refractory advanced prostate cancer.” *Id.* at 39 (citing Ex. 1004, Abstract, 1177–79).

Petitioner reasons that the “motivation to add prednisone to the method of treating prostate cancer of [Barrie] is clearly 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.” *Id.* (citing Ex. 1004, Abstract, 1177–79). Thus, 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 abiraterone acetate as a more effective CYP17 inhibitor than ketoconazole and the combination of ketoconazole and prednisone as safe and effective to treat patients with hormone refractory metastatic prostate cancer.” *Id.* at 7 (citing Ex. 1002 ¶¶ 45–49).

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. *Id.* at 40–45.

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. 12–65. We address each in turn.

a. Patent Owner's First Argument

Patent Owner argues, first, that the “central premise of Petitioner's flawed arguments is that abiraterone acetate and ketoconazole act in the same manner and would have been assumed to have the same hormonal side effects.” PO Resp. 13. Rather, Patent Owner argues, “ketoconazole and abiraterone acetate have very different mechanisms of action and do not act in the same way,” and these differences “mean that a POSA would not have translated the clinical experience with ketoconazole to abiraterone acetate.” *Id.* (citing Ex. 2038 ¶¶ 103, 122–23; Ex. 2090, 2413–14, Ex. 2018, 90; Ex. 1020, 544). Because “abiraterone acetate was understood *not* to suppress production of *all* adrenal steroids” and because “abiraterone acetate was not a ‘potent inhibitor’ of glucocorticoids,” one of ordinary skill in the art “would not have found it appropriate to simply apply the clinical experience with ketoconazole, including its side effects, and methods of managing those side effects, to abiraterone acetate.” *Id.* at 15–17 (citing Ex. 2038 ¶¶ 103–04).

Patent Owner argues next that O'Donnell confirms that abiraterone acetate allows cortisol to be made in normal levels in patients, unlike ketoconazole. *Id.* at 17. In view of the data in O'Donnell, Patent Owner argues, a person of ordinary skill in the art would have understood “that there was no need for glucocorticoid replacement therapy” and that the decision to give glucocorticoid replacement would not have been made lightly. *Id.*

at 18–19 (citing Ex. 1003, 2322–23; Ex. 2038 ¶¶ 107–15; Ex. 2040 ¶¶ 13–15, 30–35, 59–62). Regarding the Synacthen test administered in O’Donnell, Patent Owner argues that these results “lack any significance” because, *inter alia*, the Synacthen test “only measures a patient’s cortisol levels in response to stress.” *Id.* at 20–21 (citing Ex. 2040 ¶¶ 27–29, 31–34).

Patent Owner argues, finally, that Barrie confirms that abiraterone acetate acts differently from ketoconazole. *Id.* at 22. Barrie reports that administration of ketoconazole to mice caused an increase in adrenal weight, whereas administration of abiraterone acetate resulted in no significant effect in adrenal weight, indicating that “abiraterone acetate acts differently from ketoconazole and its mechanism of action was much more selective.” *Id.* at 22–23 (citing Ex. 2040 ¶ 45; Ex. 1005, 25:46–48).

Petitioner agrees that the prior art “including Barrie and O’Donnell, disclose that (1) the CYP 17 enzyme has two separate activities in the adrenal androgen synthesis pathway, a 17 α -hydroxylase and a C 17,20 lyase activity, and (2) [abiraterone acetate] is a more selective and potent inhibitor of both CYP 17 activities than ketoconazole.” Reply 2–3. Petitioner, nevertheless, replies that one of ordinary skill in the art “would have expected that cortisol deficiency from administration of [abiraterone acetate] to treat prostate cancer would diminish adrenal reserve and potentially cause adrenal insufficiency (AI), particularly during times of physiological stress.” *Id.* at 3–4 (citing Ex. 1003, 2323; Ex. 1093 ¶¶ 20–24).

Petitioner further replies that O’Donnell “expressly states that the administration of AA to treat a patient with prostate cancer may require co-administration of a glucocorticoid as replacement therapy based on abnormal cortisol responses in *all* patients in Study C.” *Id.* at 5 (citing Ex. 1003, 2321,

2323). Petitioner challenges Patent Owner's "attempts to argue that [O'Donnell's] clear statements do not actually mean what they say" and Patent Owner's arguments that a person of ordinary skill in the art would have "disregarded [O'Donnell's] unequivocal teachings, performed their own analysis of the underlying data, and reached a contrary conclusion." *Id.*

Based on the information presented during trial, we understand that ketoconazole and abiraterone acetate do not have identical mechanisms. *See, e.g.,* Ex. 1003, 2318, Figure 1. As noted by both Petitioner and Patent Owner, however, abiraterone acetate and ketoconazole are both CYP17 inhibitors. PO Resp. 5; Reply 2. 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. 29; Tr. 28:19–24; Ex. 1003, 2318. Patent Owner agrees that abiraterone acetate "inhibits cortisol to an extent." Tr. 29:10–14. Although Patent Owner urges us to focus on the differences in the mechanisms of operation of ketoconazole and abiraterone acetate (PO Resp. 13–17), 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.,* Tr. 14:20–15:5; Ex. 1003, 2318, Figure 1; Ex. 1188, 168:22–169:23. 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. For example, 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. Patent Owner's expert testified that ketoconazole, as "an inhibitor of steroid biosynthesis that had been used at that point," was a basis for comparison: "When you write scientific papers, you always like to make comparisons with what is known and explain why your results are different or the same or what the caveats are. And I think that's setting up . . . to understand what comes next, why they did this experiment." Ex. 1188, 169:15–23. 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.

Regarding the interpretation of O'Donnell's Synacthen test, we do not agree with Patent Owner that the results "lack any significance." *See* PO Resp. 20. 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 do not give a complete picture of a patient's glucocorticoid production." PO Resp. 21. We, however, 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 results for the Study C patients were "unquestionably abnormal" and implied that abiraterone acetate could result in chronic cortisol deficiency "for which glucocorticoid replacement therapy could be required." Reply 6–7 (citing Ex. 1093, 22, 68; Ex. 1023, 1245). 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.

b. Patent Owner's Second Argument

Patent Owner argues that there is no prior art evidence that ketoconazole causes mineralocorticoid excess. PO Resp. 23. Gerber does

not mention mineralocorticoid excess, Patent Owner argues, nor do any of the prior art references relied upon by Petitioner's expert, Dr. Serels. *Id.* at 24–25. Rather, Patent Owner argues, one of ordinary skill in the art would expect that ketoconazole's suppression of "all adrenal steroid synthetic pathways" would lead to a mineralocorticoid reduction. *Id.* at 26 (citing Ex. 2040 ¶¶ 36, 38; Ex. 2067, 585). Patent Owner also argues that there is no prior art evidence that abiraterone acetate would cause mineralocorticoid excess. *Id.* at 26. Neither Barrie nor O'Donnell, Patent Owner notes, measures mineralocorticoid excess. *Id.*

Patent Owner argues, finally, that even if mineralocorticoid excess was a problem, it would not be treated with prednisone. *Id.* at 28. Rather, contends Patent Owner, it would be treated with other readily available drugs, such as eplerenone, anti-hypertensives, diuretics, and potassium supplements. *Id.* at 28–29 (citing Ex. 2038 ¶ 155–56; Ex. 2040 ¶¶ 61–62; Ex. 2066, 84–85; Ex. 2037, 211:8–20).

Petitioner replies that mineralocorticoid excess is predictable from abiraterone acetate's mechanism of action. Reply 4, 7, 10. Petitioner argues that one of ordinary skill in the art would have expected that abiraterone acetate suppression of steroid synthesis "downstream of CYP 17 would increase adrenal steroids upstream of CYP17, including mineralocorticoids such as DOC and weak glucocorticoids such as corticosterone." *Id.* at 4 (citing Ex. 2040 ¶ 33; Ex. 1188, 126:10–129:4; Ex. 1093 ¶ 25). Petitioner further argues that a person of ordinary skill in the art "would have considered, by analogy, the clinical presentation of patients with combined congenital CYP 17 deficiency for guidance with respect to the anticipated clinical symptoms and appropriate options for managing such symptoms in

patients administered AA to treat mCRPC” as Patent Owner’s expert, “Dr. Auchus, has opined outside of this proceeding.” *Id.* (citing Ex. 1085, 508; Ex. 1188, 126:10–129, 4; Ex. 1023, 1243–45, Fig. 1; Ex. 1002 ¶¶ 31–32; Ex. 1093 ¶¶ 24–25). Analogizing in this manner to congenital CYP17 deficiency (*id.*), Petitioner replies that low-dose glucocorticoid replacement therapy was the “cornerstone of therapeutic management of symptoms” in patients with combined congenital CYP17 deficiency. *Id.* at 11. Petitioner also disputes that the readily available drugs identified by Patent Owner would address the underlying cortisol deficiency, criticizing eplerenone as “new” and “inadvisable” and mineralocorticoid antagonists as “counterproductive and dangerous.” *Id.* at 11–12.

On the record before us, Petitioner has reasonably established that one of ordinary skill in the art would have looked at mineralocorticoid production in the CYP17 inhibition scheme to assess the possibility of mineralocorticoid imbalance in the administration of abiraterone acetate. *See* Ex. 1002 ¶¶ 31–32; Ex. 1093 ¶¶ 25. In addition, Petitioner has reasonably established that one of ordinary skill in the art would have analogized to congenital CYP17 deficiency to assess the possibility of mineralocorticoid excess in patients administered abiraterone acetate. *See* Ex. 1002 ¶ 31–32; Ex. 1085, 508; Reply 4. Even though the analogy is not necessarily perfect or complete, an analogy to the problems arising from a congenital CYP17 deficiency likely would shed light on CYP17 inhibition in other, non-congenital situations. *Id.* We are not persuaded that the lack of explicit discussion of mineralocorticoid excess in Barrie, Gerber, or O’Donnell would discourage the analogy.

Patent Owner argues that Dr. Serels’s conclusion that ketoconazole would cause mineralocorticoid excess was incorrect. PO Resp. 24.

However, we do not understand Petitioner’s argument for motivation to combine to be premised on this assertion alone. *See* Pet. 6, 26, 37–39. Dr. Serels’s response that he now fully appreciates that “mineralocorticoid excess would not occur with ketoconazole” does not change his opinion that “cortisol deficiency would have been expected to have significant negative clinical impact in mCRPC patients treated with abiraterone” or that one of ordinary skill in the art “would have been motivated to co-administer a glucocorticoid, and in particular prednisone, as a first choice to suppress predicted ACTH drive in patients administered abiraterone acetate to treat mCRPC.” Ex. 1095 ¶ 10. 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 12 (citing Ex. 1093 ¶¶ 20–24, 26–27, 34–35).

c. Patent Owner’s Third Argument

Patent Owner argues that the prior art “discouraged the use of glucocorticoids in prostate cancer therapy unless they were clinically needed” and that a person of ordinary skill in the art “would have avoided prescribing them unless there was a clear and compelling clinical need warranting their use.” PO Resp. 29–30. First, Patent Owner argues, use of glucocorticoids such as prednisone was avoided due to their many negative side effects, such

as osteoporosis, immunosuppression, and hypertension, which are particularly detrimental to patients with mCRPC. *Id.* at 30 (citing Ex. 2038 ¶ 124; Ex. 2040 ¶ 60; Ex. 2068, 239, 242; Ex. 2069, 139). Second, Patent Owner argues that the prior art taught that prednisone could fuel the prostate cancer by indiscriminately binding to and activating the androgen receptor. *Id.* at 32 (citing Ex. 2038 ¶ 132; Ex. 2024, Abstract).

Petitioner replies that Patent Owner’s expert, outside of this proceeding, has opined that “low-dose prednisone with [abiraterone acetate] is not associated with the adverse safety profile sometimes seen when treating other malignancies and autoimmune disorders with therapeutic glucocorticoid doses.” Reply 10 (citing Ex. 1086, Abstract, 1235; Ex. 1188, 153:22–154:10). Moreover, Petitioner replies, the concern with side effects from long-term administration of glucocorticoids would not have been a factor “because of the short survival prospects for patients with mCRPC (less than two years) and the enhanced risk of immediate and potentially fatal consequences if glucocorticoid replacement therapy was not co-administered.” *Id.* (citing Ex. 1091 ¶ 40; Ex. 1093 ¶¶ 23, 28, 29). Petitioner also argues that Patent Owner’s proposed alternative options, such as another mineralocorticoid antagonist, spironolactone, potassium canrenoate, or eplerenone, were unstudied and/or dangerous. *Id.* at 11–12. Thus, “the prudent option to manage the predictable impact on adrenal reserve would have been co-administration of glucocorticoid replacement therapy.” *Id.* at 12 (citing Ex. 1093 ¶¶ 20–24, 26–27, 34–35).

We find that the prior art does not discourage or teach away from administration of prednisone to mCRPC patients. 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, but rather, as Petitioner argues, encourage exploration of such a combination. *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”). 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. 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.

d. Patent Owner’s Fourth Argument

Patent Owner argues that Petitioners “misled the Panel” regarding the prior art’s teachings about the use of ketoconazole and prednisone, in that Gerber does not teach any “relative success of administration of ketoconazole together with prednisone.” PO Resp. 33–34. First, Patent Owner argues that Gerber did not establish that co-administration of ketoconazole and prednisone is a safe and effective treatment for prostate cancer. *Id.* at 34. Patent Owner criticizes Gerber as not being akin to a clinical trial and as

providing “minimal, if any, guidance with respect to efficacy in the treatment of prostate cancer.” *Id.* at 35. Second, Patent Owner argues that the intervening prior art between 1990 and 2006 taught that ketoconazole and prednisone therapy was not a safe and effective treatment for prostate cancer. *Id.* at 37. In the early 2000s, Patent Owner argues, Phase II and III studies had failed to show any survival benefit in mCRPC, and in 2006, ketoconazole was considered a “last resort” therapy for patients who had failed to meet all other available options. *Id.*

Petitioner maintains that Gerber and other teachings in the art demonstrate that co-administration of ketoconazole and prednisone is safe and effective to treat prostate cancer. Reply 1, 9. Petitioner replies that Gerber teaches that “ketoconazole ‘as a single agent has limited use’” but a subgroup of mCRPC patients may “derive significant benefit” from the “combination of ketoconazole and physiological glucocorticoid replacement therapy.” *Id.* at 9 (quoting Ex. 1004, 1179).

We disagree that Petitioner’s arguments and evidence are misleading. 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. Tr. 9:10–14. 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.

2. Patent Owner’s Arguments as to Petitioner’s Failure to Meet Its Burden

a. Motivation to Combine

Patent Owner argues that (1) O’Donnell does not provide a motivation to use prednisone with abiraterone acetate to treat prostate cancer; (2) Barrie does not provide a motivation to use prednisone with abiraterone acetate to treat prostate cancer; and (3) Gerber does not provide a motivation to use prednisone with abiraterone acetate to treat prostate cancer. PO Resp. 39–43. Regarding O’Donnell, Patent Owner argues that, given the differences in the mechanism of action between ketoconazole and abiraterone acetate, one of ordinary skill in the art “would not have translated the clinical experience with ketoconazole to abiraterone acetate.” *Id.* at 40. Regarding Barrie, Patent Owner argues that Barrie “says nothing about glucocorticoid replacement or prednisone with any of the many compounds disclosed.” *Id.* at 42. Regarding Gerber, Patent Owner argues that Petitioner’s “flawed syllogism is scientifically inaccurate” and “misrepresents the state of the art at the time of the invention.” *Id.* at 43. Additionally, Patent Owner argues

that the prior art taught, as a whole, that for the clinical use of abiraterone acetate, glucocorticoid replacement was not required. *Id.*

In both its grounds, Petitioner states that the “motivation to add prednisone to a method of treating prostate cancer in a human patient that includes abiraterone acetate is clearly 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. 38. Thus, the absence of alleged motivation 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 for continuous use of abiraterone acetate in treating a prostate cancer in a human patient.” *Id.* 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. Regarding Gerber, we are persuaded, as we have discussed above, that Petitioner has neither presented a scientifically inaccurate syllogism, nor misrepresented the state of the art at the time of the invention. Thus, we are persuaded that Petitioner has met its burden to demonstrate motivation to combine.

b. Reasonable Expectation of Success

Patent Owner argues that, based on the prior art, one of ordinary skill in the art “had no reasonable expectation of success in arriving at the ’438 patented invention.” PO Resp. 45. More particularly, Patent Owner argues that Petitioner has not met its burden to establish that the prior art “provides a reasonable expectation that prednisone could be used for ‘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 46. 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. 45–46. 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 as an 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 17 α -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.

c. Unpredictability of Drug Combination Therapy

Patent Owner argues that the unpredictability of drug combination therapy “precludes a finding that a reasonable expectation of success with abiraterone acetate and prednisone can be gleaned from the prior art Gerber disclosure of ketoconazole and prednisone.” PO Resp. 49.

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 reasonable expectation of success 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.

d. Hindsight

Finally, Patent Owner argues that Petitioner's attempt to "narrow the problem to be solved at the time of the invention by focusing on the use of abiraterone acetate to treat prostate cancer" is a "legally improper use of hindsight." PO Resp. 52. Patent Owner characterizes the field of treatment strategies for prostate cancer as much broader, and focused on docetaxel-based chemotherapy regimens. *Id.* at 51–52.

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.

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. 48–59.

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. 53–60. Patent Owner argues that the objective indicia of non-obviousness demonstrate: 1) skepticism and the failure of others; 2) unexpected results; 3) the claimed invention has met a long-felt need; and 4) the claimed invention has achieved significant commercial success. *Id.* at 53–65.

In its Reply, Petitioner presents arguments related to commercial success and unexpected results. Reply 12–23.

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. Skepticism and the Failure of Others

Patent Owner describes the history of abiraterone acetate development as a series of starts and stops. PO Resp. 53–54. The sponsor of the research described in O’Donnell, according to Patent Owner, lost interest and shuttered the development program by 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 54–55. Petitioners do not present

any arguments directed to skepticism and the failure of others. *See* Petition *passim*; Reply *passim*.

“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.

b. Unexpected Results

Patent Owner asserts that unexpected results are demonstrated by the Phase I/II study in which abiraterone acetate was administered as a monotherapy and also together with dexamethasone, a glucocorticoid. PO

Resp. 55–56 (citing Ex. 2015). In this study, “unexpectedly, when a glucocorticoid was added to the treatment regimen after a patient stopped responding to abiraterone acetate monotherapy, many of the patients started responding again, regardless of whether that patient’s disease had worsened while on glucocorticoids in the past.” *Id.* at 56. 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 58–59. Patent Owner concludes that it was “extraordinarily unexpected” that, in Phase III trials, “the combination further demonstrated an unexpected survival benefit in patients with advanced prostate cancer.” *Id.* at 59.

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 additionally clinically significant anti-cancer benefit.” Pet. 53. 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 56. In the Reply, Petitioner argues that the Response (1) does not compare the closest prior art (O’Donnell and/or Barrie); (2) draws conclusions from irrelevant data and makes improper comparisons; (3) ignores its own data that shows the combination of

abiraterone acetate and prednisone is not better; and (4) ignores the data that prednisone may contribute to drug resistance to abiraterone acetate.

Reply 12–19.

Regarding Patent Owner’s comparison of abiraterone acetate monotherapy with abiraterone acetate/dexamethasone therapy, we agree with Petitioner that from those studies Patent Owner is “drawing the conclusion that there is an unexpected result of abiraterone acetate with prednisone. But the claims are to prednisone. Not to dexamethasone.” Tr. 22:10–13.

Although dexamethasone and prednisone are both glucocorticoids (Tr. 45:14–16), Patent Owner does not point us to any evidence as to why the ordinary artisan would consider dexamethasone and prednisone to be interchangeable for the purpose of comparing results. 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. *Cf.* Tr. 42:15–43:3.

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.

c. Long-Felt Need

According to Patent Owner, prior to the invention claimed in the '438 patent, "mCRPC was considered incurable and the prognosis for men with the disease was dismal," and thus, "there was an urgent need for new agents that would improve survival." PO Resp. 59–60.

In the Petition, Petitioner argues that "the combination of abiraterone acetate and prednisone satisfied no long-felt need beyond what abiraterone may have done," because (1) "any success of Zytiga[®] that is not a result of the claimed invention is irrelevant to secondary considerations"; (2) "the combination of abiraterone acetate and prednisone does not produce unexpected results in anti-cancer benefit"; and (3) "the perception among clinicians is that the requirement to coadminister prednisone with Zytiga is a drawback to its use to treat prostate cancer." Pet. 56–57 (citing Ex. 1017 ¶¶ 31–35; Ex. 1002 ¶¶ 74, 80, 83, 85).

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. 1017 ¶ 33; Ex. 2038 ¶ 196. 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 alone.” PO Resp. 60. Patent Owner criticizes Dr. McDuff’s declaration, which “contends that ZYTIGA[®]’s commercial success is of limited ‘economic relevance’ due to other factors” as a “mischaracterization of the evidence regarding commercial success of ZYTIGA[®].” *Id.* To support its argument, Patent Owner presents evidence of market share. Tr. 55:19–23 (citing Ex. 2044 ¶¶ 39–43). Patent Owner also presents evidence that abiraterone acetate is administered together with prednisone at least 89% of the time. *Id.* (citing Ex. 2044 ¶ 47; Ex. 2095).

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. 50. Petitioner also argues that (1) applicants “adduced no evidence that a market consisting only of ‘post chemo’ mCRPC patients is the appropriate relevant market;” (2) “recent market data demonstrate a steep and continuous decline in Zytiga’s market share post-Xtandi launch;” and (3) “any commercial success of Zytiga[®] is likely due to the effectiveness of abiraterone acetate in treating prostate cancer.” *Id.* at 50–51. 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 57 (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 and (2) that Petitioner fails to establish any causal nexus to the '438 claims.

Reply 20–22. Petitioner also argues that the market performance of Zytiga heavily derives from factors other than the subject matter of the '438 patent, such as patient convenience. *Id.* at 22–23; Tr. 20:6–11. Petitioner does not materially dispute the \$1.07 billion annually in sales figure.

“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. 60. 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. 64 (citing Ex. 2044 ¶ 36; Ex. 2005 ¶ 8); Tr. 47:1–7. 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 ¶¶ 68–70, 74–78. 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. 40–48; Ex. 1002 ¶¶ 50–66.

F. Motion to Exclude

Patent Owner filed a Motion to Exclude (Paper 70), to which Petitioner responded (Paper 76) and to which Patent Owner filed a Reply (Paper 79). 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 1017, 1017 [B-1 and B-2], 1032, 1040–67, 1088, 1091 ¶¶ 23–29, 32–34, 42, 44–46 and 72–74, 1092, 1093 ¶ 13, 1094, 1097–1156, 1160–63, 1165–73, and 1175–90. Paper 70, 14. 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) exhibits that Petitioner belatedly filed in connection with the Reply and declarations; (c) sections of Petitioner's Reply

declarations that are not cited in the briefs, and therefore irrelevant and prejudicial; and (d) exhibits that lack authenticity or violate the hearsay rule. *Id.* at 1.

Petitioner responds that (a) Exhibits 1017 and 1096 (currently 1152) and related exhibits cited therein are proper reply evidence; (b) Exhibits to the Reply Brief filed and served after midnight should not be stricken; (c) Patent Owner has cited no authority for its position that an uncited paragraph should be stricken; and (d) Exhibits 1040, 1041, 1048, 1049, 1051–53, 1055–57, 1088, 1128, 1130, 1140, and 1166, as well as 1017 [B-1 and B-2], 1032, 1042–44, 1058–63, 1067, and 1140, have been authenticated, and Exhibits 1042–44, 1055, 1056, 1058–63, and 1067 are not hearsay under FRE 803. Paper 76, 1–9.

Because we do not expressly rely upon Exhibits 1017 [B-1 and B-2], 1032, 1040–67, 1088, 1092, 1094, 1097–1151, 1153–56, 1160–63, 1165–73, and 1175–87, 1189, and 1190 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 1017, 1096 (1152), 1091, 1093, and 1188.

We disagree that Exhibit 1017 (Dr. McDuff’s first declaration) should be excluded. 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 further credit Petitioner’s argument that “the Patent Owner itself attempted to claim commercial success as an objective indicia of non-obviousness in Patent Owner’s Response.” Paper 76, 2. We also disagree that Exhibit 1092 (Dr. McDuff’s second

declaration, in fact Exhibit 1152) is inadmissible pursuant to 37 C.F.R. § 42.123(b), or that it is improper reply evidence. Petitioner may submit evidence with its Reply in support of Petitioner's properly responsive arguments. *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1078 (Fed. Cir. 2015). In particular, Petitioner also notes that the second McDuff Declaration, now labeled as Exhibit 1152, was cited to as Exhibit 1096 in the Reply and, thus, was in fact cited to in the Reply. Paper 76, 3. The most recent Exhibit List filed by Petitioner indicates that Exhibit 1096 is "Reserved" and Exhibit 1152 is in fact the second declaration of Dr. McDuff. Paper 75, 18. We find that Exhibits 1017 and 1096 (1152) are properly part of the record.

Regarding Exhibit 1188, a late action will be excused either on a showing of good cause or upon a Board decision that consideration on the merits would be in the interests of justice. 37 C.F.R. § 42.5(c)(3). This rule must be construed to secure the just, speedy, and inexpensive resolution of every proceeding. 37 C.F.R. § 42.1(b). Weighing the prejudice to Petitioner of the delay in filing Exhibit 1188 against the prejudice to Petitioner of not considering Exhibit 1188, we determine that it would be in the interests of justice to excuse Petitioner's late action. We note that there is no statutory bar in this instance, and that Petitioner filed the Reply and certain primary supporting documents in a timely manner, and sought to obtain Patent Owner's leave to retroactively extend the deadline for filing the reply by one day, which Patent Owner declined. Paper 76, 4–5.

Regarding the portions of Exhibits 1091 and 1093 that were not specifically cited in Petitioner's reply, 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 Reply, as filed, references Exhibits 1091 and 1093 in its List of Exhibits. Paper 62, 10. Exhibits 1091 and 1093 were filed along with the Reply. We find the reference to the Declaration 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. Thus, the portions of Exhibits 1091 and 1093 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 1017, 1096 (1152), 1091 ¶¶ 23–29, 32–34, 42, 44–46 and 72–74, 1093 ¶ 13, and 1188 and *dismissed* as to Exhibits 1017 [B-1 and B-2], 1032, 1040–67, 1088, 1092, 1094, 1097–1151, 1153–56, 1160–63, 1165–73, and 1175–87, 1189, and 1190.

G. Motion to Seal

Patent Owner filed a number of documents in this proceeding as “Parties and Board Only.” *See, e.g.*, Exhibits 2038, 2044, 2092–94, 2118. Patent Owner also filed a Protective Order (Exhibit 2113) and a Red-line of Protective Order (Exhibit 2114). Neither party, it appears, filed a motion to seal.

A party intending for a document to be sealed must file a motion to seal with a proposed protective order. *See* 37 C.F.R. §§ 42.14, 42.54(a). If such a motion were to be granted, the Board would consider entry of the modified protective order, which would govern the treatment of confidential information in the proceeding. If Patent Owner seeks to seal the documents

filed as “Parties and Board Only,” Patent Owner shall file a motion to seal within ten (10) business days of the entry of this Decision. *See* 35 U.S.C. § 316(a)(1); 37 C.F.R. §§ 42.14, 42.54(a); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,770 (Aug. 14, 2012).

H. 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 1017, 1096 (1152), 1091 ¶¶ 23–29, 32–34, 42, 44–46 and 72–74, 1093 ¶ 13, and 1188 and *dismissed* as to Exhibits 1017 [B-1 and B-2], 1032, 1040–67, 1088, 1092, 1094, 1097–1151, 1153–56, 1160–63, 1165–73, and 1175–87, 1189, and 1190; 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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