United States Court of Appeals for the Federal Circuit

BTG INTERNATIONAL LIMITED, JANSSEN BIOTECH, INC., JANSSEN ONCOLOGY, INC., JANSSEN RESEARCH & DEVELOPMENT, LLC,

Plaintiffs-Appellants

v.

AMNEAL PHARMACEUTICALS LLC, AMNEAL PHARMACEUTICALS OF NEW YORK, LLC, DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., WOCKHARDT BIO AG, WOCKHARDT USA LLC, WOCKHARDT LTD., MYLAN PHARMACEUTICALS INC., MYLAN INC., WEST-WARD PHARMACEUTICALS CORP., nka Hikma Pharmaceuticals USA Inc., HIKMA PHARMACEUTICALS LLC, TEVA PHARMACEUTICALS USA, INC.

Defendants-Appellees

PAR PHARMACEUTICAL, INC., PAR PHARMACEUTICAL COMPANIES, INC., RISING PHARMACEUTICALS, INC.,

Defendants

No. 2019-1147

Appeals from the United States District Court for the District of New Jersey in Nos. 2:15-cv-05909-KM-JBC, 2:16-cv-02449-KM-JBC, and 2:17-cv-06435-KM-JBC, Judge Kevin McNulty.

BTG INTERNATIONAL LIMITED, JANSSEN BIOTECH, INC., JANSSEN ONCOLOGY, INC., AND JANSSEN RESEARCH & DEVELOPMENT, LLC,

Plaintiffs-Appellants

v.

AMERIGEN PHARMACEUTICALS, INC., AMERIGEN PHARMACEUTICALS LIMITED,

Defendants-Appellees

No. 2019-1148

Caption continued on inside cover

Appeal from the United States District Court for the District of New Jersey in No. 2:16-cv-02449-KM-JBC, Judge Kevin McNulty.

JANSSEN ONCOLOGY, INC.,

Appellant

V.

AMERIGEN PHARMACEUTICALS LIMITED, ARGENTUM PHARMACEUTICALS LLC,

Appellees

No. 2019-1323

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-00286 and IPR2016-01317.

JANSSEN ONCOLOGY, INC.,

Appellant

V.

MYLAN PHARMACEUTICALS INC., AMNEAL PHARMACEUTICALS LLC, AMNEAL PHARMACEUTICALS OF NEW YORK, LLC, DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., TEVA PHARMACEUTICALS USA, INC., WEST-WARD PHARMACEUTICAL CORPORATION, HIKMA PHARMACEUTICALS LLC,

Appellees

No. 2019-1324

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-01332 and IPR2017-00853.

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JANSSEN ONCOLOGY, INC.,

Appellant

v.

WOCKHARDT BIO AG,

Appellee

No. 2019-1325

Appeal from the United States Patent and Trademark Office,
Patent Trial and Appeal Board in No. IPR2016-01582.

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January 22, 2019

CERTIFICATE OF INTEREST

I, Constantine L. Trela, Jr., counsel for Plaintiffs-Appellants Janssen Biotech, Inc., Janssen Oncology, Inc., and Janssen Research & Development, LLC, certify the following:

1. The full name of every party or *amicus* represented by me is:

Janssen Biotech, Inc., Janssen Oncology, Inc., and Janssen Research & Development, LLC

2. The name of the real party in interest (if the party named in the caption is not the real part in interest) represented by me is:

N/A

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Janssen Biotech, Inc. and Janssen Oncology, Inc. are wholly owned subsidiaries of Johnson & Johnson, which is a publicly held corporation. No other publicly held corporation owns 10% or more of the stock of Janssen Oncology, Inc.

Janssen Research & Development, LLC is a wholly owned subsidiary of Centocor Research & Development, which is a wholly owned subsidiary of Janssen Biotech, Inc., which is a wholly owned subsidiary of Johnson & Johnson, which is a publicly held corporation. No other publicly held corporation owns 10% or more of the stock of Janssen Research & Development.

4. The names of all law firms and the partners or associates that appeared for the party or *amicus* now represented by me in the trial court or agency or are expected to appear in this court (**and who have not or will not enter an appearance in this case**) are:

Sidley Austin LLP: Bindu Donovan, Todd L. Krause, Lisa A. Schneider, S. Isaac Olson, H. Ashley Chi, Andrew T. Langford**,** Amanda A. Potter, Jesselyn C. Pe

Akin Gump Strauss Hauer & Feld: Dianne B. Elderkin, Barbara L. Mullin, Ruben H Munoz

Robinson Miller LLC: Donald A. Robinson, Keith J. Miller, Justin T. Quinn, Michael J. Gesualdo

Desmarais LLP: Bindu Donovan

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal.

BTG International Limited, et al. v. MSN Pharmaceuticals Inc. & MSN Laboratories Private Ltd., Civil Action No. 18-02372-KM-JBC (D.N.J.); *Janssen Biotech, Inc. et al. v. Mylan Pharms., Inc. et al.*, Civil Action No. 1:15-cv-00130 (N.D. W.Va.); *BTG International Limited, et al. v. Qilu Pharmaceutical Co., Ltd. & Qilu Pharma, Inc.,* Civil Action No. 2:18-cv-16521 (D.N.J.).

Dated: January 22, 2019

Respectfully submitted,

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CERTIFICATE OF INTEREST

I, Anthony C. Tridico, counsel for Plaintiffs-Appellants BTG International Ltd., certify the following:

1. The full name of every party or *amicus* represented by me is:

BTG International Limited

2. The name of the real party in interest (if the party named in the caption is not the real part in interest) represented by me is:

N/A

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

BTG International Ltd. is a subsidiary of BTG plc. BTG plc is a publicly held corporation that holds 100% of BTG International (Holdings) Ltd, which in turns owns 100% of BTG International Ltd.

4. The names of all law firms and the partners or associates that appeared for the party or *amicus* now represented by me in the trial court or agency or are expected to appear in this court (**and who have not or will not enter an appearance in this case**) are:

Robinson Miller LLC: Donald A. Robinson, Keith J. Miller, Justin T. Quinn, Michael J. Gesualdo

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal.

BTG International Limited, et al. v. MSN Pharmaceuticals Inc. & MSN Laboratories Private Ltd., Civil Action No. 18-02372-KM-JBC (D.N.J.); *Janssen Biotech, Inc. et al. v. Mylan Pharms., Inc. et al.*, Civil Action No. 1:15-cv-00130 (N.D. W.Va.); *BTG International Limited, et al. v. Qilu Pharmaceutical Co., Ltd. & Qilu Pharma, Inc.,* Civil Action No. 2:18-cv-16521 (D.N.J.).

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STATEMENT CONCERNING CONFIDENTIAL MATERIAL

Pursuant to Fed. Cir. R. 28(d)(2)(B), Janssen Biotech, Inc., Janssen Oncology, Inc. and Janssen Research & Development, LLC state that the confidential material redacted on pages Appx318, Appx319, Appx320, Appx321 of the Addendum concerns certain identity and third-party information that was redacted by the Patent Trial and Appeal Board from the public version of its decision.

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STATEMENT OF RELATED CASES

These consolidated actions have not previously been before this or any other appellate court. Counsel for Appellants believes the following cases will directly affect or be directly affected by this Court's resolution of the consolidated appeals:

BTG International Limited, et al. v. MSN Pharmaceuticals Inc. & MSN Laboratories Private Ltd., Civil Action No. 18-02372-KM-JBC (D.N.J.);

Janssen Biotech, Inc. et al. v. Mylan Pharms., Inc. et al., Civil Action No. 1:15-cv-00130 (N.D. W.Va.);

BTG International Limited, et al. v. Qilu Pharmaceutical Co., Ltd. & Qilu Pharma, Inc., Civil Action No. 2:18-cv-16521 (D.N.J.).

JURISDICTIONAL STATEMENT

The district court appeals (Nos. 2019-1147 and 2019-1148) arise from Hatch-Waxman Act suits brought by Plaintiffs-Appellants BTG International Limited, Janssen Oncology, Inc., Janssen Biotech, Inc., and Janssen Research & Development, LLC (collectively, "Janssen"). The district court had jurisdiction under 28 U.S.C. §§ 1331, 1338. The court entered a Rule 54(b) judgment on October 26, 2018, which was amended on October 30. Plaintiffs timely appealed. Defendants' cross-appeals were dismissed on December 21, 2018. This Court has jurisdiction under 28 U.S.C. § 1295(a).

The Board appeals (Nos. 2019-1323, 2019-1324, and 2019-1325) arise from Final Written Decisions issued on January 17, 2018 in three *inter partes* review (IPR) proceedings. The Board had jurisdiction under 35 U.S.C. §§ 311, 316(c). Janssen timely requested rehearing, which the Board denied on December 3, 2018. Janssen timely appealed. This Court has jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

STATEMENT OF ISSUES

The Board appeals present the following issues:

1. Whether the Board erred by construing "treating" and "treatment" of prostate cancer to cover a therapy that has no anti-cancer effect.

2. Whether the Board's claim construction and other errors warrant vacatur of its obviousness determination.

The district court appeals present the following issues:

1. Whether the district court was permitted to consider obviousness challenges that had already been resolved in Final Written Decisions of the Board, notwithstanding 35 U.S.C. § 315(e)(2)'s bar on litigation of grounds for invalidity raised in an IPR that results in a "final written decision under section 318(a)."

2. In the alternative, whether the district court's obviousness determination should be vacated because the court applied the wrong legal standards in assessing motivation to combine, reasonable expectation of success, and objective indicia of non-obviousness.

INTRODUCTION

These appeals involve a breakthrough treatment for advanced prostate cancer. Before the invention of U.S. Patent No. 8,822,438 ("the '438 patent"), patients faced a dismal prognosis, with death likely within 12-18 months and few meaningful treatment options. The invention claimed by the '438 patent changed this picture dramatically. Its method of treating advanced prostate cancer with a combination of abiraterone acetate ("abiraterone") and prednisone offered patients a striking increase in survival and transformed researchers' understanding of the causes of the disease. The invention was counter-intuitive, and it has been a runaway commercial success.

The invention was made in the face of enormous skepticism—not just among academic researchers, but among major pharmaceutical companies, including one that abandoned its rights to abiraterone and others that were offered rights and passed. Researchers at the time were focused in an entirely different direction, generally on chemotherapy-based treatments. Secondary hormonal therapies like the claimed invention were not being pursued and were disparaged as futile and antiquated. The inventors defied expectations and conventional wisdom and produced a cancer treatment that was, and remains, state of the art—a treatment so dramatically successful that the FDA granted it expedited approval three times and the market granted it preeminent status and billions in sales.

The decisions before the Court in these appeals dismiss this life-changing and medical practice-changing invention as obvious, a merely routine step well within the skill of ordinary artisans. They reached this illogical conclusion as a result of fundamental legal errors that this Court can and should correct.

The Board's IPR decisions started with an erroneous claim construction that conflicted with both the claim language and an express definition in the specification (as well as the construction adopted by the district court). The claims require a combination therapy in which each specified component "treats" cancer, yet the Board effectively read this requirement out of the claims. This legal error wholly undermined the Board's obviousness analysis, both because the Board never found that skilled artisans would have had a reasonable expectation of success in achieving the invention *as claimed*, and because the Board's analysis of the nexus between the objective evidence of non-obviousness and the claimed invention rested on its misunderstanding of what invention was claimed. These legal errors require vacatur.

The district court also determined that the invention was obvious, but the court erred by even reaching this issue. Once the Board resolved Defendants' obviousness challenges in Final Written Decisions, 35 U.S.C. § 315(e)(2) barred the court from considering those challenges. Notwithstanding the statute's plain text and unequivocal legislative history, the court refused to apply the statutory bar

based primarily on what the court saw as policy concerns. But those concerns were misplaced and, more fundamentally, cannot override the plain statutory text. The court's obviousness determination should therefore be reversed, and because the court otherwise resolved infringement and validity in Janssen's favor, this Court should direct entry of judgment for Janssen.

Even if § 315(e)(2) did not preclude the district court from addressing obviousness, its decision still cannot stand. The court's analysis was plagued by legal error. Although it properly construed the claims, the court applied the wrong legal standard in assessing motivation to combine and reasonable expectation of success. Indeed, it failed even to consider whether—much less explain why—a skilled artisan would have chosen to pursue development of a combination therapy involving abiraterone in the first place, particularly when hundreds of other paths had been identified as more promising at the time and major pharmaceutical companies had affirmatively passed on abiraterone. Moreover, the court reached a conclusion on obviousness before even considering the objective indicia of non-obviousness, and when it considered objective indicia, it shifted the burden to Janssen to disprove obviousness. In other words, the district court adopted the very mode of analysis that this Court rejected in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1075 (Fed. Cir. 2012), and its progeny.

STATEMENT OF THE CASE

I. The '438 Patent's Life-Extending Discovery

Prostate cancer is the second leading cause of cancer death in American men, trailing only lung cancer. Metastatic prostate cancer, in which the cancer has spread to other organs, is particularly deadly. Appx758.

The traditional first-line treatment for metastatic prostate cancer is to deprive the cancer cells of androgen hormones, such as testosterone, that those cells need to proliferate. Appx21447-21449. Such "androgen deprivation therapy," or "ADT," involves either surgical castration or the administration of drugs to stop androgen production by the testes. Appx21448-21451. ADT is not a cure, however, and eventually stops being effective in almost all patients, at which point the cancer resumes growing. Appx21449. Prostate cancer that reaches this stage is called metastatic castration-resistant prostate cancer, or "mCRPC." Appx21449-21450.

In 2006, at the time of the invention, the mechanisms underlying prostate cancer's progression to a castration-resistant state were poorly understood, resulting in great uncertainty as to how to combat it. Appx21017-21019, Appx22763, Appx22768-22769, Appx22793-22795. Researchers had spent decades developing and testing hundreds of different agents with diverse mechanisms of action to attempt to find a treatment, without success. Appx22764,

Appx22766-22773, Appx28488-28495, Appx28505-28514, Appx28532-28537, Appx28555-28559, Appx28560-28570, Appx27916-27935. Other than the cytotoxic chemotherapy docetaxel, which caused terrible side effects, all failed to improve survival. Appx22764-22765. So the search continued.

The prevailing view among researchers by 2006 was that the progression of prostate cancer in mCRPC patients was likely independent of the hormones targeted in first-line ADT treatment. Appx21018; *see* Appx87. Because numerous attempts to develop effective second-line hormonal therapies—*i.e.*, therapies aimed at further reducing hormone levels in a patient who has already received ADT—had failed to produce any survival benefit, Appx22465, Appx22552-22553, researchers hypothesized that the cancer cells adapted to grow without androgens, Appx21018.

The view that such secondary hormonal therapies would not be efficacious was reflected in the terms "hormone-refractory prostate cancer" and "androgen-independent prostate cancer," used at the time to describe the status of mCRPC patients. Appx21018, Appx22764, Appx22793-22795. Thus, by 2006, researchers widely believed that further reductions in androgens below castrate levels would have no clinical benefit in treating mCRPC, and had generally moved away from studying second-line hormonal therapies. Appx21138-21142, Appx22773-22776, Appx28523-28531, Appx27876-27879. This applied in particular to ketoconazole,

an anti-fungal hormonal compound which had been tried as a second-line prostate cancer treatment without success. Appx28546, Appx22829, Appx22817, Appx22827-22834, Appx22176-22177, Appx22552, Appx28705. Researchers at the time concluded that "the next generation of clinical trials should not be futile hormonal manipulations." Appx28529.

Instead, researchers were exploring a wide variety of different therapeutic strategies and pharmacological agents. *See, e.g.*, Appx22767, Appx28488-28495, Appx28560-28570, Appx27916-27935. Indeed, as of 2006, more than 200 compounds for treating mCRPC were in development. Appx28488. A 2005 paper surveying the "most promising agents in clinical development" listed many of these compounds and did not include any second-line hormonal therapy. Appx28560-28570, Appx22769-22770.

Abiraterone, a second-line hormonal compound, was discovered in 1992 at London's prestigious Institute of Cancer Research ("ICR"). Abiraterone blocks the adrenal glands and testes from producing testosterone and other androgens. Appx22886, Appx27737-27755. From 1995 to 1999, abiraterone was licensed to Boehringer Ingelheim, which sponsored the first clinical studies. Appx21143-21144, Appx21147, Appx22887. These Phase I trials focused on abiraterone's safety and effect on testosterone production, not its efficacy in treating prostate cancer. Appx21146, Appx21132, Appx22785, Appx22787, Appx23171-23180.

Boehringer abandoned abiraterone as the studies ended, and the researchers who conducted them had difficulty getting their results published. Appx21022, Appx21138-21142, Appx21144-21145, Appx22887. Over the next five years, ICR's licensing partner, BTG, attempted to license abiraterone to numerous pharmaceutical companies, including major companies like Wyeth and Bristol-Myers Squibb, but none was interested. Appx21022, Appx21025-21026, Appx21147, Appx21145-21146, Appx22887. Finally, in 2004, a small California start-up, Cougar Biotechnology, Inc., took a license. Appx21146-21147.

Around that same time, Dr. Johann de Bono joined ICR to focus on finding an effective prostate cancer therapy. Appx21007. Despite then-conventional wisdom that mCRPC was androgen-independent, Cougar enlisted Dr. de Bono's help in testing abiraterone's efficacy in mCRPC patients. Appx21024. As he was designing the first Cougar clinical trial, Dr. de Bono had an insight that led to the invention of the '438 patent. He hypothesized that abiraterone, while decreasing androgen production, might increase other, non-androgenic steroids and that those steroids might promote the growth of prostate cancer cells—in effect making cancer resistant to abiraterone. Dr. de Bono further hypothesized a way to overcome this resistance and enhance and prolong the efficacy of abiraterone (to the extent it was shown to have any). Adding a glucocorticoid such as dexamethasone or prednisone, he thought, could decrease production of these other

steroids and thereby reverse any resistance to abiraterone. *See generally* Appx21041-21051, Appx28341, Appx28429.

These insights were remarkable. Secondary hormonal therapies in general were viewed as futile. Abiraterone in particular had never been tested for efficacy, and no one had even hypothesized that patients taking abiraterone would develop resistance, much less identified a way to overcome it. Appx21052-21053. Glucocorticoids were approved for inflammation and for palliation of patients with certain unrelated cancers, but not for treatment of any cancer, and prednisone in particular had never been shown to provide a survival benefit in prostate cancer patients. Appx21771, Appx22562, Appx22818, Appx28072-28089. Indeed, as Defendants' expert conceded at trial in the district court, neither he nor other physicians believed that prednisone provided an anti-cancer benefit at the time of the invention. Appx22169-22170, Appx22176. Thus, the notion that abiraterone could be combined with a glucocorticoid like prednisone and that the two compounds in combination would both provide an anti-cancer benefit was wholly unexpected.

Notwithstanding this, Dr. de Bono designed a study that first tested the efficacy of abiraterone alone on prostate cancer, and then added an "extension" phase in which patients whose disease progressed on abiraterone also received a glucocorticoid. Appx21041-21052. The first study used dexamethasone, the

glucocorticoid used most frequently in England, though Dr. de Bono believed prednisone would work the same way. Appx21048-21049. The extension study was an unprecedented success. Some patients in the trial had been taking dexamethasone prior to the study as a palliative, with no durable effect on their cancer. They discontinued dexamethasone before they started taking abiraterone, and their cancers were controlled or reduced for a time with abiraterone alone. But just as Dr. de Bono predicted, they eventually developed resistance to abiraterone, and their cancers resumed progressing. The subsequent co-administration of a glucocorticoid with abiraterone dramatically reversed the resistance in many patients, confirming Dr. de Bono's hypothesis. *See generally* Appx21059-21060, Appx21066-21086, Appx27936-27946, Appx27952-27960.

Building on the results of the extension study, Dr. de Bono and his team conducted further studies in which abiraterone and prednisone were co-administered from the beginning of treatment. Appx21095-21104, Appx21186-21189, Appx21192-21193, Appx21194-21195. The results underscored the unique benefits of the combination. For example, in Phase II studies, the combination more than doubled the time that patients responded, measured by time to PSA progression—an indicator of prostate cancer growth—and provided a larger proportion of patients with long-term progression-free survival relative to patients in an earlier study treated with abiraterone alone. Appx21544-21545. Similarly,

two Phase III clinical trials in which mCRPC patients were co-administered abiraterone and prednisone demonstrated a dramatic overall survival benefit. Appx21569-21573; *see also* Appx21195-21196.

These results were extraordinary. As one researcher wrote, they "dramatically alter[ed] our view of hormonal treatment in advanced-stage prostate cancer." Appx28551, Appx22899-22900. The abiraterone-prednisone combination was the first non-cytotoxic, second-line hormonal therapy to receive FDA approval and extend overall survival and progression-free survival in mCRPC patients. Appx22888-22889. The FDA has thrice recognized the breakthrough nature of the therapy by approving ZYTIGA (Janssen's abiraterone product) in combination with prednisone under its priority review program, which allows expedited review of therapies that would provide significant improvements in the safety or effectiveness of treatment of serious conditions. Appx21308-21310. The market has likewise recognized the therapy's innovativeness by rewarding ZYTIGA with enormous commercial success. Appx22704-22713, Appx28185-28192, Appx28193-28200, Appx28223-28232, Appx29060-29068.

II. The '438 Patent and Asserted Claims

The '438 patent embodies Dr. de Bono's surprising discovery that the concomitant administration of prednisone with abiraterone is an effective treatment to combat advanced prostate cancer, in which both prednisone and abiraterone

have an anti-cancer effect when used in combination. Claim 1, the '438 patent's only independent claim, provides:

> 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.

Appx765. Based on express definitions in the specification, the district court construed the term "therapeutically effective amount" to mean "an amount effective for treating cancer," and the terms "treatment" and "treating" to mean "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." Appx4052-4081, Appx4082-4083. The Board, by contrast, concluded that the terms "treatment" and "treating" were open-ended and included any effect, even one that had no impact on the cancer at all. Appx30-31.

III. Procedural Background

Defendants filed abbreviated new drug applications ("ANDAs") to market generic abiraterone products with labeling substantively identical to ZYTIGA's—*i.e.*, calling for concomitant administration of abiraterone and prednisone. As part of their ANDAs, Defendants certified that the '438 patent is invalid or will not be infringed. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 21 C.F.R. § 314.95. In response,

Janssen filed suit under 35 U.S.C. § 271(e)(2), asserting that Defendants will induce or contribute to infringement of the '438 patent. Each Defendant sought *inter partes* review.

A. District Court Proceedings

In response to Janssen's infringement claims, Defendants asserted, among other defenses, that the '438 patent is invalid as obvious.

After the Board issued Final Written Decisions in the IPRs, Janssen moved *in limine* under 35 U.S.C. § 315(e)(2) to preclude Defendants from asserting their obviousness challenges because Defendants had admittedly raised those same challenges in the IPRs and thus were now statutorily barred from pursuing them in district court. *See* Appx12776 (Defendants presented "the same three invalidity grounds" to the Board); Appx20999. The court denied Janssen's motion. Appx20944; *see also* Appx19008-19009.

On October 26, 2018, the court issued its Opinion (Appx1-71) and Order (Appx144-145), concluding that (1) the '438 patent is invalid for obviousness; (2) the '438 patent has an adequate written description; and (3) assuming the '438 patent were valid, Defendants' marketing of generic abiraterone products would induce and contribute to infringement. Appx74. In a footnote, the court reaffirmed its holding that § 315(e)(2) does not bar Defendants' obviousness challenges, although the court acknowledged that § 315(e)(2) "may be read" to do

just that. The court asserted—without citing any statutory language or legislative history—that the "manifest statutory intent" is to prevent only unsuccessful IPR petitioners from relitigating invalidity claims. Appx98.

In holding that the asserted claims of the '438 patent are invalid as obvious, the court first found that "abiraterone had been identified in the prior art as a second-line prostate cancer treatment." Appx115. According to the court, two references—Barrie 1994 and O'Donnell 2004—suggested that abiraterone could be used as a second-line therapy. Appx114. Although the court agreed with Janssen that the "prevailing belief" at the time of invention (*i.e.*, years later, in 2006) "was that, once [prostate] cancer resumed growing after ADT, the cancer became androgen independent," Appx87, it concluded that such evidence merely established that abiraterone was not the most promising potential therapy, Appx121. The court did not address Janssen's argument that, at the time of invention, a skilled artisan would not have selected abiraterone in the first place.

The court next found a motivation to combine abiraterone with prednisone, Appx116, and also found that a skilled artisan would expect the drugs could be combined with a reasonable probability of success, Appx118. The court did not specifically address whether a person of ordinary skill in 2006 would have expected both abiraterone and prednisone to have an anti-cancer effect in a combination therapy. Nor did the court address the critical admission of

Defendants' expert that he "do[es] not recall ever feeling that there was any proven anti-cancer benefit for prednisone." Appx22169-22170, Appx22173-22174; *see also* Appx22170 ("physicians that [he] was in contact with also didn't have a sense that there was any proven anti-cancer benefit" from prednisone).

The court then turned to secondary considerations—not to inform its analysis of obviousness in the first instance, but rather to determine whether the "objective considerations presented" by Janssen "alter[ed] [its] conclusion" of obviousness. Appx118. First, the court explained away ZYTIGA's massive commercial success as the product of a patent on abiraterone itself that supposedly blocked others from pursuing abiraterone-based therapies. Appx118-120. The court discounted the fact that Boehringer, which had rights under that patent and was not "blocked," never made the invention, but instead abandoned its rights after the unsuccessful Phase I studies. It also discounted evidence that the patent had thereafter been made widely available for licensing. According to the court, Janssen failed to show that the licensing efforts were more than merely "lackluster" and "desultory," Appx120, even though the efforts included broadly advertising the availability of a license to any interested company and directly contacting various pharmaceutical giants. Appx21022, Appx21145-21146, Appx21147.

Second, the court found the market skepticism factor to be "neutral." Appx121. The court acknowledged evidence of skepticism, but stated that "[m]uch of that skepticism seems to be directed to abiraterone itself, rather than the claimed combination." Appx121. The court did not explain why someone skeptical of abiraterone would not also be skeptical of, much less pursue, a combination therapy in which it was a key component.

Third, the court addressed evidence of long-felt but unmet need and unexpected results. The court found that ZYTIGA plus prednisone yielded a survival benefit sixty percent longer than the existing FDA-approved therapies—four months versus two-and-a-half—but dismissed that improvement as "incremental" and a difference "'merely in degree,'" not "'in kind.'" Appx122 (citation omitted). The court said nothing about the undisputed evidence that ZYTIGA plus prednisone was better tolerated and less toxic than other therapies. Appx22896. Nor did the court address the fact that this therapy "really changed the standard of care" for those with advanced prostate cancer, Appx21103-21104, Appx21576-21577 (invention "was practice changing"); *see also* Appx22898-22900, Appx28551-28554, or that the FDA's multiple priority review approvals for ZYTIGA demonstrated that the invention produced significant improvements in patient care.

Finally, the court found that professional approval of ZYTIGA plus prednisone "weighs somewhat" in favor of non-obviousness. Appx123. Nevertheless, the court found that, on balance, the "foreshadow[ing]" of the combination in the prior art "favors a conclusion of obviousness." Appx123.

The court amended its Opinion on October 31, 2018. Appx72-143. The court's conclusions regarding validity and infringement were unchanged, but the court amended its discussion of § 315(e)(2) to opine that the pendency of rehearing requests before the Board made the statutory bar inapplicable.

B. Agency Proceedings

The three IPR proceedings—*Amerigen*, *Mylan*, and *Wockhardt*—raised largely identical issues, and the Final Written Decisions likewise are substantially identical.

1. *Amerigen*

The *Amerigen* IPR rested on three references: O'Donnell (2004 article reporting the Phase I abiraterone safety studies from the 1990s), Gerber (1990 article regarding use of ketoconazole and prednisone), and Barrie (1997 patent directed to a class of compounds that includes abiraterone).[1] *See* Appx181-182; Appx187-188. Amerigen's theory was that a skilled artisan would have pursued

[1] The *Amerigen* and *Argentum* IPRs were later joined and resolved in a single Final Written Decision. *See* Appx29523-29527.

abiraterone to treat prostate cancer based on the disclosures of either O'Donnell or Barrie, and would have added prednisone to address anticipated side effects of abiraterone, as Gerber had done with ketoconazole. Appx189-191.

A central issue was whether one of ordinary skill in 2006 would have had a reasonable expectation of success in achieving the invention as claimed. That turned in large part on claim construction: none of Amerigen's primary references suggested that prednisone would "treat" cancer—*i.e.*, have an anti-cancer effect—even on its own, let alone in combination with abiraterone. And at the institution stage, it appeared that the Board agreed with Janssen that "treat," "treating," and "treatment" required "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." Appx156.

In its Final Written Decision, however, the Board explained that its understanding of "treatment" was much broader. In the Board's view, a drug could "treat" cancer "perhaps by an anti-cancer effect, or perhaps by some other mechanism." Appx208. Based on that broader construction, the Board ruled, for example, that Amerigen was not required to show a reasonable expectation that prednisone would have an anti-cancer effect. Appx204-206.

The Board's broad construction rested on two premises. First, the Board noted that the specification suggests that steroids "may have anti-cancer effects,"

but they may "also have other therapeutic effects." Appx207. Second, the Board believed that the patent's use of "include" in its definition of "treatment" made the term entirely open-ended, covering any effect, even one that had no impact on cancer at all. *See* Appx30-31. Based on this construction, the Board concluded that Amerigen "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." Appx208. The Board did not find—because its construction did not require it to find—that a skilled artisan in 2006 would have had a reasonable expectation of success in achieving a combination therapy in which *both* prednisone *and* abiraterone have an anti-cancer effect. *See, e.g.*, Appx208 ("Claim 1 … does not require a particular result.").

Janssen presented extensive objective indicia evidence, but the Board concluded that none of it supported non-obviousness. Appx210-220. Its analysis was largely driven by its claim construction, for in assessing the required nexus, the Board viewed the "claimed invention" through the lens of its broad construction of "treatment." Thus, for example, the Board failed to consider that while it might not have been unexpected that prednisone would have a palliative effect of some kind when co-administered with abiraterone, *see* Appx207-208, Appx276, Appx359, that it would have an anti-cancer effect was completely unexpected in 2006, Appx30206-30207, Appx37325, Appx44592.

2. *Mylan*

The *Mylan* IPR was filed after *Amerigen* and asserted the same grounds for invalidity,[2] Appx243, and the two Final Written Decisions are largely identical.

3. *Wockhardt*

The *Wockhardt* IPR involved an obviousness challenge based on the Gerber and O'Donnell references combined with a third reference, Sartor—a 1998 article that reported modest and short-lived PSA declines in a retrospective analysis of 29 patients on prednisone. *See* Appx330-331, Appx45665-45669. The Board rejected Janssen's claim construction for the same reasons it did in *Amerigen* and *Mylan*. Appx356-359. The Board made an additional finding, based on Sartor, that "prednisone would 'treat' prostate cancer" in the sense of having an anti-cancer effect. Appx359. But the Board did *not* find that a skilled artisan in 2006 would have had a reasonable expectation of success in achieving a combination therapy in which abiraterone and prednisone both have an anti-cancer effect. Again, as in *Amerigen* and *Mylan*, the Board read "the language of the challenged claims" to "not require a particular result." Appx359.

The Board's treatment of objective indicia in *Wockhardt* likewise mirrored *Amerigen* and *Mylan*. *See* Appx360-371. Again, the Board's decision to give the

[2] The *Mylan* and *Actavis* IPRs were later joined and resolved in a single Final Written Decision. *See* Appx35389-35394.

objective indicia no weight was driven by its understanding that the claimed invention did not require each component of the combination therapy to have an anti-cancer effect.

SUMMARY OF ARGUMENT

The Board Appeals. The Board's decisions turn on an erroneous claim construction. The claims cover methods for "treating" cancer, but on the Board's reading, the methods need not have any effect on cancer at all. This construction conflicts not only with the claim language but also with the explicit definition of "treating" and "treatment" in the specification. According to the patent, the "treatment" provided by a compound must "include" one of a number of specifically identified anti-cancer effects. The Board's decision renders this definition meaningless. In the Board's view, the word "include" means that a compound can provide *either* an enumerated anti-cancer effect *or* some other, non-enumerated, effect.

The Board's erroneous construction infected its obviousness analysis. For example, the Board did not even consider whether a skilled artisan would have had a reasonable expectation of success in achieving the inventions of the '438 patent *as claimed*, because the Board did not have the right claimed inventions in mind. That both abiraterone and prednisone would have anti-cancer effects in a combination anti-cancer therapy was entirely counter-intuitive in 2006.

Researchers at the time of the invention had identified hundreds of promising compounds for treating advanced prostate cancer, and although both abiraterone and prednisone were known, neither was among the promising candidates on its own, much less in combination. To the contrary, as of 2006, secondary hormonal therapies like abiraterone were viewed as wholly ineffective, and those in the field did not regard prednisone as an anti-cancer treatment at all. The Board was able to bypass this issue because its construction would cover a therapy in which prednisone had some other therapeutic effect, and the Board's passing suggestion that its assessment would be the same under either construction of "treatment" cannot be squared with either the Board's actual analysis or the undisputed record.

The erroneous construction similarly infected the Board's analysis of objective indicia. As the Board noted, the "weight accorded the objective evidence" depends on the nexus between that evidence and the claimed invention—*i.e.*, the invention as defined by the claim construction. Appx211. Because of its erroneous construction, the Board failed to evaluate the nexus between the actual invention—that is, the invention defined by the correctly construed claims—and the objective evidence demonstrating that the actual invention was not obvious. For example, the Board concluded that the claimed invention did not meet a long-felt need in part because, in the Board's view, the invention was a therapy "based on abiraterone," which had been available long

before 2006. Appx215. But the invention is not merely the administration of abiraterone; it is a particular combination in which abiraterone and prednisone both have a specific anti-cancer effect. Had the Board appreciated that the invention involves a combination in which two drugs both have anti-cancer effects, it would have properly attributed the dramatic survival benefits of the ZYTIGA-prednisone therapy, the unexpected results, and the enormous commercial success to the claimed invention.

The District Court Appeals. The district court's judgment that the '438 patent is invalid as obvious rests on several critical legal errors, each of which warrants reversal or vacatur.

I. The court erred at the outset by allowing Defendants to pursue their obviousness challenges. Defendants presented these same challenges in the IPRs, and the Board resolved them in Final Written Decisions. Section 315(e)(2) therefore barred Defendants from pursuing those same obviousness challenges in district court. The court acknowledged that the plain terms of § 315(e)(2) could be read to preclude Defendants' challenges, but it disregarded the statute's language based on its view of the policies it believed motivated Congress to enact the provision. Contrary to the court's policy views, nothing in § 315(e)(2) limits its scope to petitioners who are unsuccessful, nor is there any suggestion in the

legislative history that Congress intended, but forgot to include, such a limitation. The statute is clear and should be applied as written.

Congress created IPRs as an alternative to district court litigation. In doing so, Congress gave parties a choice: they can pursue prior art challenges in an IPR to a final written decision, or in a district court, but not both. If a challenger elects to take advantage of the lower standard of proof and swifter time-to-decision available on the IPR path, and the IPR results in a final written decision, the challenger is precluded from pursuing the same challenge in court.

Whether rehearing requests are pending at the agency is irrelevant. Not only have those requests now been resolved, but nothing in the text or legislative history suggests that rehearing requests bear on the application of § 315(e)(2). The statute's text states that a final written decision issued under § 318(a) triggers the bar—not a "final appealable decision" or "final agency action."

II. Even if the district court could address obviousness, this Court should vacate the decision because it rests on legal errors. At the outset, the district court failed to identify any reason a skilled artisan would have decided to pursue development of abiraterone as of 2006. As Janssen showed, the scientific community at that time believed that second-line hormonal therapies like ketoconazole and abiraterone were not worth pursuing and would not address what was believed to be the core issue with advanced prostate cancer. The district court

acknowledged this, explicitly finding that the "prevailing belief" at the time of invention "was that, once [prostate] cancer resumed growing after ADT, the cancer became androgen independent." Appx87. Nonetheless, the court accepted Defendants' invitation to simply assume a skilled artisan would start with abiraterone. This Court, however, has instructed courts to identify a reason why a skilled artisan would select a particular starting point. The district court erred by failing to do that.

The court compounded its error by concluding that a person of ordinary skill would have had a reasonable expectation of success without ever deciding, as the law requires, whether that person would have had a reasonable expectation of success in achieving "what is claimed" by the patent—namely, a combination therapy in which both abiraterone and prednisone have anti-cancer effects. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1365-67 (Fed. Cir. 2016). Nor could the court have made such a finding. Defendants' own expert admitted that the sole prior art reference the court discussed did not show prednisone could treat prostate cancer and that practitioners at the time did not view it as a cancer treatment.

Finally, the court's approach to evaluating objective indicia of non-obviousness has been squarely and repeatedly rejected by this Court. The district court concluded that the combination of abiraterone and prednisone was obvious,

and only then turned to objective indicia. In doing so, the court shifted the burden to Janssen to disprove its obviousness conclusion, as the court's approach to each individual indicium confirms.

STANDARD OF REVIEW

In the Board appeals, this Court reviews legal issues *de novo* and underlying factual determinations for substantial evidence. *PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC*, 815 F.3d 747, 751 (Fed. Cir. 2016). The primary issue in the Board appeals is claim construction. Where, as here, the Board's construction is based on the intrinsic evidence, this Court reviews claim construction *de novo*. *See id.*

The threshold issue in the district court appeals is the scope of 35 U.S.C. § 315(e)(2). Statutory interpretation is a matter of law, which this Court reviews without deference. *See Res-Care, Inc. v. United States*, 735 F.3d 1384, 1387 (Fed. Cir. 2013). The Court reviews the legal conclusion of obviousness *de novo* and the underlying factual findings for clear error. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1354 (Fed. Cir. 2013).

ARGUMENT

I. The Board's Decisions Rest on an Erroneous Claim Construction.

A. The Claimed Invention Is a Combination Therapy in Which Both Abiraterone and Prednisone Have Anti-Cancer Effects.

Every claim in the '438 patent concerns a "method for the treatment of a prostate cancer" that involves administering a "therapeutically effective" amount of abiraterone and a "therapeutically effective" amount of prednisone. Appx765-766. As the Board recognized, a "therapeutically effective" amount is an amount that is "effective for *treating* prostate cancer." Appx333 (emphasis added). This means that both the abiraterone and the prednisone must "treat" the prostate cancer. But in the Board's view, "treating" cancer does not require any effect on the cancer itself—"some other mechanism," such as "palliative effects," can also qualify. Appx359.

The Board's unbounded construction cannot be squared with the intrinsic record. To "treat" cancer within the meaning of the '438 patent, a drug must have an effect on the cancer itself, such as by controlling the growth of a tumor or minimizing or delaying the spread of cancer cells. Treating something other than the cancer cannot suffice. That is how the district court construed the claims, Appx4081, and it is the only reasonable construction in light of the claim language and specification.

1. "Treatment" Requires An Anti-Cancer Effect.

The claim language makes clear that what is being "treated" is cancer rather than, for example, the side effects of a cancer therapy. *See Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335, 1344 (Fed. Cir. 1998) ("actual words of the claim are the controlling focus"). Every claim recites a "method for the *treatment of a prostate cancer*." Appx765-766 (emphasis added). Several of the claims go a step further, reciting a method for treating cancer that "is not responding to at least one anti-cancer agent," which further confirms that the purpose of the claimed therapy is to generate an anti-cancer response—even when other drugs have failed. *See* Appx765-766 (claims 13-17, 20). Yet under the Board's construction of "treating" and "treatment," neither the prednisone nor even the abiraterone needs to have any anti-cancer effect at all—providing a patient with palliative therapy alone is enough to practice the patented invention. But if the inventors had intended to claim methods for treating pain suffered by cancer patients, the side effects of a therapy, or something else altogether, they could have done so. *See* Appx4066 (district court noting that "the patent refers to treatment of cancer, as opposed to patients *with* cancer"). They did not do that: they claimed a "method for the treatment of a prostate cancer." Appx765-766; *see Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (words of the claim are "generally given their ordinary and customary meaning").

Any doubt on this score is resolved by the specification. Most importantly, the specification provides an express definition of the disputed terms. In a section titled "Definitions," the patent explains:

> As used herein, and unless otherwise defined, the terms "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.

Appx759(3:46-50). The patent thus defines "treating" and "treatment" to require direct effects on the growth or spread of the cancer itself. A therapy need not have all of these anti-cancer effects to qualify as a "treatment," but it must have at least one anti-cancer effect. When patentees act as lexicographers, their "lexicography governs." *Phillips*, 415 F.3d at 1316. Here, that means "treating" requires having some effect on the cancer itself.

The patent provides ample evidence beyond this express definition that the invention is directed to treating the cancer itself. The title of the patent is "Methods and Compositions for Treating Cancer," and the Background emphasizes the need for "effective anti-cancer treatment options." Appx755, Appx758(2:1-4). The Detailed Description specifies that a CYP17 inhibitor (such as abiraterone) should be used in "an amount that is sufficient to treat *the cancer*," Appx761(7:34-36) (emphasis added), and it likewise specifies that a steroid (such as prednisone) should be used in "an amount that is sufficient to treat *the cancer,*"

Appx762(10:21-24). Indeed, cancer is the only condition requiring treatment mentioned anywhere in the patent. *Kinetic Concepts, Inc. v. Blue Sky Med. Grp.*, 554 F.3d 1010, 1018-19 (Fed. Cir. 2009) (giving "wound" a narrow construction to fit specification's description); *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1375 (Fed. Cir. 2009) (construing "spike" consistent with specification use); *Edwards Lifesciences LLC v. Cook Inc.*, 582 F.3d 1322, 1329-30 (Fed. Cir. 2009) (construing "graft" to mean the only devices described in the specification). The patent nowhere even mentions pain reduction, palliation, or any other therapeutic effects.

2. The Board's Contrary Reasoning Does Not Withstand Scrutiny.

In the Board's view, treatment "can 'include' a number of actions," such that "prednisone may be used to 'treat' prostate cancer, perhaps by an anti-cancer effect, or perhaps *by some other mechanism*," such as "palliative effects." Appx359 (emphasis added). The Board never explains how one would determine whether a given "other mechanism" would qualify as "treatment"—it may be that any effect on the body would suffice. *Cf. Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp.*, 93 F.3d 1572, 1578 (Fed. Cir. 1996) (refusing construction that would render a limitation "meaninglessly empty"). What is clear, however, is that one could practice the claimed method for treating cancer as the Board understands it without having any effect on the cancer at all.

The Board's erroneous construction rests primarily on its misreading of two aspects of the specification. First, the Board leans heavily on the word "include" in the express definition of "treating" and "treatment." Appx359 ("[B]ecause '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."). As the Board saw it, "include" made the definition entirely open-ended, sweeping in any conceivable therapeutic (or non-therapeutic) effect on a cancer patient, without regard for whether the "treatment" affected the cancer at all. That was a clear legal error. As the district court recognized in its claim construction decision, this Court has made clear that "includes" or "including" cannot "somehow trump[] consideration of the specification and prosecution history and displace[] application of standard claim construction principles." Appx4071 (quoting *Lochner Techs., LLC v. Vizio, Inc.*, 567 F. App'x 931, 939 (Fed. Cir. 2014) (non-precedential)). Based on the intrinsic record, "include" should be read as requiring one of the specified effects; otherwise, "treating" has no boundaries and thus no definition. Appx4072 (holding that "include" does not "do the work of extending the scope of a patent to matters not discussed therein.").

But even if one were to set aside the intrinsic evidence and read "include" as non-limiting, it still could not support the boundless construction the Board adopted. The "plain meaning" of "including," this Court has held, is that the

"named elements are essential, but other elements may be added." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1344-45 (Fed. Cir. 2003); *see also Liberty Ammunition, Inc. v. United States*, 835 F.3d 1388, 1400 (Fed. Cir. 2016); *Lucent Techs., Inc. v. Gateway, Inc.*, 525 F.3d 1200, 1214 (Fed. Cir. 2008). Here, where the list of enumerated elements uses the disjunctive "or," the invention need not include all of those elements, but it must include at least one. Simply put, "include" or "including" does not mean, as the Board thought, that any list that follows is simply exemplary or optional: the listed elements—or at least one of them where the list uses "or"—are required. *Amgen*, 314 F.3d at 1344-45.

Here, every enumerated effect in the patent's express definition targets tumors or cancer cells themselves, and no other type of therapeutic effect is mentioned anywhere. The only possible reading of this definition is that "treatment" *must* include at least one of the enumerated effects, and not that "treatment" *may* include *either* an enumerated effect *or* any other effect, regardless of whether it has anything to do with cancer cells or tumors. The Board erred in concluding that use of "include" in the definition of "treatment" means that "treatment" need not include any enumerated element.

It is no answer to say that abiraterone can treat the cancer while prednisone treats, for example, any side effects. As the Board acknowledged, both the abiraterone and the prednisone must be administered in a "therapeutically

effective" amount, *i.e.*, an amount "effective for treating prostate cancer." Appx333. "Treating prostate cancer" cannot reasonably be understood to have two different meanings in a single claim. *See Aventis Pharm. Inc. v. Amino Chems. Ltd.*, 715 F.3d 1363, 1380 (Fed. Cir. 2013) ("same claim term in the same patent ... [presumptively] carries the same construed meaning"). If "treating" means that one component must have an anti-cancer effect, the other component must have an anti-cancer effect as well.

Second, the Board relies on what it saw as a distinction in the specification between "an anti-cancer agent" and "a steroid." Appx356. But the fact that a steroid may have uses other than as an anti-cancer agent is beside the point. The specification identifies "antibiotic[s]" as anti-cancer agents, Appx761, and specifically identifies prednisone as an antibiotic, Appx762. Moreover, the specification makes clear that, in the invention as claimed, the steroid should be used in "an amount that is sufficient to treat the cancer," Appx762(10:21-24), and the Board correctly interpreted "therapeutically effective amount of prednisone" to mean "an amount of prednisone effective for treating prostate cancer." Appx333. And the express definition of "treating," as explained, requires having some effect on the cancer itself. The distinction on which the Board relied does not exist.

The Board's construction of "treating" is thus erroneous in light of the claim language and specification. *See PPC Broadband*, 815 F.3d at 755 ("[B]roadest

reasonable interpretation must be reasonable in light of the claims and specification."). Under the Board's construction of "treatment," neither abiraterone nor prednisone needs to have an anti-cancer effect, contrary to the entire purpose of the claimed invention.

B. The Board's Erroneous Construction Infected Its Analysis of Obviousness.

The Board's claim construction error undermines the Board's entire obviousness analysis.

As the Board acknowledged, abiraterone was "underutiliz[ed]" and the subject of "skepticism until the application for the '438 patent was filed in 2006." Appx366, Appx364. Indeed, by 2006 those in the field believed that secondary hormonal therapies (like abiraterone) had failed, and thus used terms such as "hormone-refractory" or "androgen-independent" prostate cancer to describe mCRPC. Appx42587-42588; *see also* Appx45780 (noting, in 2002, that there was "no evidence that secondary hormonal therapies ... improve survival"); Appx42988 (recommending, in 1999, that "[t]he next generation of clinical trials" not "consist of futile hormonal manipulations"). The counter-intuitive hypothesis that led to the inventions of the '438 patent was that a glucocorticoid such as prednisone could produce an anti-cancer effect when co-administered with abiraterone. Appx43560-43561. Dr. de Bono's investigation into this hypothesis led to the breakthrough discovery of the combination therapy claimed in the '438 patent and

approved on a priority basis by the FDA—a therapy that has led to a dramatic survival benefit for advanced prostate cancer patients and has been a runaway commercial success.

Based on its erroneous construction—that a drug can "treat" cancer without having any effect on the cancer itself—the Board concluded that the claims would encompass something else: a therapy in which only abiraterone treats the cancer. Having identified the wrong invention, the Board not surprisingly reached the wrong result. It failed to appreciate, for example, that a skilled artisan in 2006 would have had no reasonable expectation of success in developing a combination therapy in which *both* abiraterone *and* prednisone treat advanced prostate cancer. Moreover, without an accurate understanding of the invention, the Board could not properly evaluate the powerful objective evidence of non-obviousness.

1. The Board Did Not Find the Required Reasonable Expectation of Success in Achieving the Invention as Claimed.

An "obviousness determination requires finding ... that the skilled artisan would have had a reasonable expectation of success" in making the claimed invention. *In re Stepan Co.*, 868 F.3d 1342, 1345-46 (Fed. Cir. 2017); *see also Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009). In administrative proceedings, the Board must expressly "articulate why a person of ordinary skill in the art would have had a reasonable expectation of success."

Stepan, 868 F.3d at 1347; *see also In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006) (Board "must articulate the basis" for its obviousness determination).

Across three decisions, the Board never found that a skilled artisan in 2006 would have had a reasonable expectation of success in making the invention as claimed, *i.e.*, a combination therapy in which *both* arbiraterone *and* prednisone have an anti-cancer effect. In each case, the Board's findings on expectation of success concerned something other than the claimed invention because of its erroneous claim construction. Appx208 ("prednisone may be used to 'treat' prostate cancer ... by some other mechanism"); Appx276 (same); Appx359 (same). The *Wockhardt* decision tacks on a conclusory finding that, based solely on the 1998 Sartor reference, "prednisone would 'treat' prostate cancer under either definition." Appx359. But that is still *not* equivalent to the necessary finding that a person of skill, at the time of invention in 2006, would have expected both prednisone and abiraterone to have an anti-cancer effect, particularly in combination.

The Board never made that finding. Instead, the Board relied on its erroneous claim construction. Appx359 (claims do "not require a particular result"). Based on that construction, the Board was not convinced that "Petitioner [had] not established"—notably, it never said Petitioners *had* established—"a reasonable expectation of achieving the challenged claims." Appx359. Even

ignoring the Board's clear misapplication of the burden of proof, this conclusion cannot stand because it is based on a misunderstanding of the "challenged claims." As this Court has explained, the "question of a reasonable expectation of success" is "tied to the proper construction of the claim language." *L.A. Biomedical Research Inst. v. Eli Lilly & Co.*, 849 F.3d 1049, 1067 n.8 (Fed. Cir. 2017) (vacating obviousness determination based on erroneous construction); *Rovalma, S.A. v. Bohler-Edelstahl GmbH & Co.*, 856 F.3d 1019, 1026 (Fed. Cir. 2017) (vacating Board decision because Board cited no evidence that showed artisans "would have reasonably expected to achieve the specific thermal conductivities recited in the claims."); *cf. Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013) ("the expectation-of-success analysis must match the highly desired goal").

Under a proper claim construction, the Board could not have found the required expectation of success. By 2006, Sartor himself had acknowledged that glucocorticoids such as prednisone had not "demonstrated a survival advantage," Appx44462, and those in the field recognized that the PSA response to glucocorticoids administered alone (which was all that Sartor 1998 reported) was generally modest and short-lived, Appx42655. Even more fundamentally, Wockhardt's own expert testified that he thought it was "unclear what the prednisone impact would be when combined with abiraterone acetate."

Appx44592; *see also* Appx30206-30207 (Amerigen expert would "not expect that the addition of prednisone to a treatment for prostate cancer that includes abiraterone would result in any clinically significant enhancement of the *anti-cancer or anti-tumor effect*, as opposed to enhancement of the safety and tolerability, of treatment"); Appx37325 (Mylan expert testifying that a person of skill would believe "that prednisone would *not* have any measurable cancer-treating effect when combined with abiraterone acetate") (emphasis added). On this record, the Board could not have found that a skilled artisan in 2006 would have expected both abiraterone and prednisone to have anti-cancer effects when administered together.

2. The Board Did Not Assess the Objective Evidence Demonstrating the Non-Obviousness of the Invention as Claimed.

The Board's erroneous construction also infected its analysis of objective indicia of non-obviousness, which "may often be the most probative and cogent evidence in the record." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). These indicia cannot be assessed without a clear and correct understanding of the scope of the claims. *See, e.g.*, *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018) ("objective evidence of non-obviousness must be commensurate in scope with the claims"). The Board recognized that the proper assessment of objective evidence depends upon the

scope of the claimed invention, Appx361, but the Board's failure to construe the claims correctly necessarily precluded it from properly assessing the objective indicia.

Because the direct consequence of the Board's construction was that prednisone need not have an anti-cancer effect in the combination, the Board focused solely on abiraterone as the inventive aspect of the invention. This led to several errors in the Board's assessment of objective indicia. For example, in assessing long-felt need, the Board noted that "drugs that contribute to increasing cancer patient survival rates nearly always satisfy a long-felt need," but it concluded that there was not sufficient evidence to support a need for the invention, in part because abiraterone's "availability (and underutilization) for approximately a decade ... undermines [the] argument that a long-felt need existed for any regimen based on abiraterone." Appx366. But that is entirely the wrong inquiry: the need was not for an abiraterone-based regimen—it was for a therapy with improved survival benefits for advanced prostate cancer patients. In any event, the claimed method for treating cancer is not a "regimen based on abiraterone" alone; it is a combination therapy in which *both* abiraterone *and* prednisone treat advanced prostate cancer. Once the scope of the claims is properly defined, the failure of abiraterone by itself to meet the long-felt need for an effective treatment only underscores the non-obviousness of the combination

therapy. Abiraterone was available for over a decade, yet the need for an effective treatment for advanced prostate cancer persisted. In contrast, the combination therapy was a breakthrough.

The Board's analysis of commercial success reflects the same legal error. Having construed the claims to cover a therapy in which abiraterone is the only drug combating the cancer itself, the Board discounted any "anti-cancer role of prednisone." Appx370. This allowed the Board to attribute ZYTIGA's unquestioned commercial success to abiraterone alone—notwithstanding abiraterone's "availability (and underutilization) for approximately a decade," Appx366—rather than to the combination therapy claimed in the '438 patent. Had the Board understood that both drugs in the combination must treat the cancer, then the fact that the commercial embodiment of the patent—ZYTIGA administered "in combination with prednisone for the treatment of patients with [mCRPC]" according to its FDA-approved label, Appx38907—was a runaway success whereas abiraterone alone was not even pursued would be powerful evidence of non-obviousness. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000) (nexus is presumed when marketed product embodies claimed features).

The Board's treatment of commercial success reflects other legal errors as well. Most importantly, the Board shifted the burden of proof onto Janssen in two

distinct ways. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007) ("burden of proof never shifts to the patentee to prove validity"). First, although the Board acknowledged that nexus was presumed, it determined that Petitioners rebutted the presumed nexus *without* finding that they had presented evidence sufficient to show that ZYTIGA's success was due to something other than the claimed invention. Appx370 (noting that it was "not clear" what drove sales, and concluding "that Petitioner present[ed] sufficient evidence to rebut the presumption of nexus."). If the record is inconclusive, the presumption cannot be displaced.

Second, the Board imposed upon Janssen the burden to show that BTG's efforts to license an asserted "blocking patent" were sufficient to "remove the deterrent effect" of that patent. Appx369. But a "blocking patent may or may not deter innovation in the blocked space," *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1338 (Fed. Cir. 2018), and the extent of a blocking patent's impact is a "fact-specific inquiry," *id.* at 1339. Janssen presented evidence (and the Board assumed) that the asserted blocking patent was "available for licensing and was actively shopped around to other companies" between 2000 and 2004. Appx368-369. Indeed, Boehringer had rights to abiraterone in the 1990s and had every incentive to develop the wildly successful inventions of the '438 patent if it was obvious to do so, but halted its entire development program three years after

taking a license. Appx42683. Against this backdrop, it was incumbent upon *Petitioners* to show that the blocking patent so deterred efforts by others in the field that ZYTIGA's tremendous commercial success should be attributed to that deterrent effect rather than the merits of the combination invention. *Cf. Pfizer*, 480 F.3d at 1359. But the Board flipped the burden, found that Janssen had not met it, and disregarded commercial success altogether.

The Board's erroneous claim construction similarly infected its evaluation of skepticism. Janssen introduced evidence that those in the field in 2006 were skeptical of secondary hormonal therapies (which would include both abiraterone and prednisone), and that many had tried and failed to develop secondary hormonal therapies that would produce a survival benefit for mCRPC patients. *See, e.g.*, Appx41696-41697 (discussing evidence). The Board refused to acknowledge this skepticism by first suggesting that the 1997 Barrie patent on abiraterone showed "at least some in the industry had overcome their skepticism." Appx365. But this is backwards. That the scientific community was skeptical of abiraterone after it was known and patented is what demonstrates the non-obviousness of a combination treatment involving abiraterone. The Board further erred by ignoring that skepticism with respect to combining two secondary hormonal treatments into a combination therapy in which both combat the cancer. This omission stems from the Board's erroneous claim construction. Only by ignoring that prednisone must

have an anti-cancer effect in the combination could the Board conclude that the skepticism toward secondary hormonal therapies did not extend to the combination of abiraterone and prednisone.

Had the Board understood that both elements in the combination therapy must have an anti-cancer effect, it would have been compelled to give the objective evidence substantial weight. The evidence showed that Boehringer, one of the world's largest pharmaceutical companies, was not "blocked," but failed to make the invention and instead abandoned efforts to develop any product involving abiraterone, Appx42683-42684, and Petitioners' own experts testified that they would not have expected prednisone to have an anti-cancer effect when administered with abiraterone. *See* Appx44592, Appx30206-30207, Appx37325. On a proper construction of the claims, skepticism surrounding secondary hormonal therapies strongly supports a finding of non-obviousness. So, too, does the fact that the combination therapy claimed in the '438 patent—in which *both* abiraterone and prednisone fight the cancer—succeeded where others had failed.

Ultimately, the Board's erroneous claim construction alone warrants vacatur and remand for the Board to determine, in the first instance, whether the inventions actually claimed in the '438 patent would have been obvious. *See, e.g.*, *PPC Broadband*, 815 F.3d at 749 (remanding in light of erroneous claim construction).

The fact that the construction infected the Board's evaluation of the evidence confirms the need for vacatur and remand.

II. The District Court Should Not Have Considered an Obviousness Challenge That Was Barred by 35 U.S.C. § 315(e)(2).

While the Board erred in its obviousness analysis, the district court erred by considering obviousness at all.

A. The Plain Language of § 315(e)(2) Precludes Defendants' Obviousness Arguments.

Section 315(e)(2) provides:

> The petitioner in an inter partes review … that results in a final written decision under section 318(a) … may not assert … in a civil action … that the claim is invalid on any ground that the petitioner raised or reasonably could have raised during that inter partes review.

35 U.S.C. § 315(e)(2). By its terms, this proscription extends to a petitioner in any IPR "that results in a final written decision under section 318(a)," regardless of whether the petitioner was successful or unsuccessful. When the Board issues a final written decision, estoppel applies and bars relitigation of the same obviousness challenges in a district court.

Here, each Defendant sought *inter partes* review of the '438 patent on several grounds, each of which was also raised in the district court—a point Defendants expressly acknowledged. Appx12776, Appx20999. Those Board proceedings "result[ed] in final written decision[s] under section 318(a)," as § 315(e)(2) requires. *See* Appx12780 (citing § 318(a)), Appx12830, Appx12880.

Therefore, § 315(e)(2) barred Defendants from asserting—and the district court from deciding—that the '438 patent is invalid as obvious in the Hatch-Waxman cases.

B. The District Court's Reasoning Confirms Its Error.

The district court rejected the conclusion compelled by the statutory text based on its own view of patent policy. But the court's policy concerns cannot override the clear statutory text and were misplaced in any event.

1. Section 315(e)(2) Applies to Successful Petitioners.

Although the statute's text draws no distinction between successful and unsuccessful petitioners, the court refused to "accept … that Congress intended to require a [successful challenger] to stand mute in court because it previously prevailed on the same issue before the PTAB." Appx98. But the statute as written does not require a successful challenger to stand mute in court. Rather, the successful challenger is simply limited to defenses not addressed or addressable in the Board proceedings. Here, for example, Defendants challenged the patent on § 112 grounds and presented their non-infringement defenses to the court without running afoul of the statute. The statute limits only their ability to pursue certain prior art defenses presented in IPR proceedings. And as to that, the statute expresses Congress's clear intent to apply the bar to *all* defendants who pursue an IPR to final written decision. When "the statute's language is plain," that is

"where the inquiry should end."[3] *Puerto Rico v. Franklin Cal. Tax-Free Tr.*, 136 S. Ct. 1938, 1946 (2016); *see also Honeycutt v. United States*, 137 S. Ct. 1626, 1635 n.2 (2017) (courts "cannot construe a statute in a way that negates its plain text").[4]

The legislative history confirms Congress's purpose. IPR preclusion was designed to be stronger than what had existed under the earlier *inter partes* reexamination regime. *See* 157 Cong. Rec. 2710 (2011) (statement of Sen. Grassley) ("strengthened estoppel standard"); 157 Cong. Rec. 13,187 (2011) (statement of Sen. Kyl) (referring to bill's "enhanced estoppels"). That earlier estoppel provision expressly applied only to unsuccessful challengers, barring them from asserting "the invalidity of any claim *finally determined to be valid and patentable* on any ground which [they] raised or could have raised during the inter partes reexamination proceedings." 35 U.S.C. § 315(c) (2006) (emphasis added).

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[3] Likewise, § 315(e)'s title ("Estoppel") "cannot limit the plain meaning of the text." *Bhd. of R.R. Trainmen v. Balt. & Ohio R.R.*, 331 U.S. 519, 528-29 (1947). In any event, "estoppel" is a general term that refers to "[a] bar that prevents the relitigation of issues"; it does not apply solely to those who litigated and lost. *See Estoppel*, Black's Law Dictionary (10th ed. 2014); *New Hampshire v. Maine*, 532 U.S. 742, 749 (2001) (applying judicial estoppel to litigant who had prevailed in prior case).

[4] The only other decision-makers to address the issue have held that § 315(e)(2) applies to all petitioners, successful or not. *See SiOnyx, LLC v. Hamamatsu Photonics K.K.*, 330 F. Supp. 3d 574, 599 (D. Mass. 2018); *Certain Hybrid Electric Vehicles & Components Thereof*, Inv. No. 337-TA-1042, at 7 n.12 (USITC Nov. 1, 2017) (Initial Determination).

But that limitation was dropped in the America Invents Act (AIA). Congress plainly knew how to limit preclusion to unsuccessful challengers, and the district court should have respected Congress's decision to drop that limitation and expand the scope of preclusion.

The expanded estoppel provision supported Congress's broader goal of creating "procedures" that would "provide faster, less costly *alternatives* to civil litigation to challenge patents." 157 Cong. Rec. 2710 (2011) (statement of Sen. Grassley) (emphasis added). As Senator Kyl put it, the AIA's expanded estoppel provision would ideally ensure that IPR proceedings would "*completely substitute* for at least the patents-and printed-publications portion of the civil litigation." 157 Cong. Rec. 3429 (2011) (statement of Sen. Kyl) (emphasis added). In the district court's view, however, an IPR is an "alternative" or "substitute" only when the challenger loses. If the challenger succeeds, the court and parties must bear the expense of litigating the same issues again. The statute and legislative history make clear that Congress intended to eliminate such waste.

Nor is there any unfairness in applying the statute as written. As noted above, contrary to the district court's concern, defendants are not required to "stand mute." Appx98. Congress gave defendants a choice of forum for certain prior art-based defenses. The IPR path offers a quicker and less expensive alternative under a more lenient standard of proof, but defendants who choose the

IPR path bear both the benefits and burdens of their choice. *See, e.g.*, *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 672-73 (1990) (interpreting statute to impose both advantages and disadvantages, not only advantages). One of those burdens is forgoing litigation of certain (but not all) defenses in the district court. Defendants who choose to pursue an IPR to final written decision remain free to assert non-infringement, written description, and other non-prior-art defenses—as Defendants here did—but they may not rehash theories that were or could have been raised before the Board.

There is no exception to this general rule for Hatch-Waxman cases. Under Hatch-Waxman, Congress carefully crafted a scheme that would encourage pioneer drug developers to undertake the massive investments necessary to discover and develop new drug products, while streamlining the process for generic entry at the appropriate time. A key feature of this scheme is 35 U.S.C. § 271(e)(4), under which district courts must enjoin the approval of a generic product found to infringe an unexpired patent under § 271(e)(2). Generic manufacturers can avoid a finding of infringement (and thus an injunction) by proving that the patent is invalid in the district court, and if they choose this path, they must prove invalidity by clear and convincing evidence. *See Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2246 (2011). But if they elect the IPR path, they cannot assert invalidity on printed prior-art grounds in the district court.

Generic manufacturers who pursue an IPR can avoid an injunction under § 271(e)(4) if the district court determines that they do not infringe or that the patent is invalid on other grounds, but otherwise the injunction is automatic—at least until a Final Written Decision of unpatentability is confirmed by this Court. The district court may disapprove of this system, *see* Appx98, but it is the system Congress enacted.

2. Section 315(e)(2) Is Triggered by a "Final Written Decision Under Section 318(a)," Not Final and Appealable Decisions or Final Agency Action.

The district court held that Janssen's then-pending rehearing requests made the Board's Final Written Decisions insufficiently "final" for § 315(e)(2) to apply, reasoning that "appealability" triggers preclusion under the statute. Appx98-99. But nothing in the statute or its legislative history suggests that appealability has any relevance at all. *See generally* Joseph Matal, *A Guide to the Legislative History of the America Invents Act: Part II of II*, 21 Fed. Cir. B.J. 539, 616 (2012) (explaining that § 315(e)(2) will "apply *as soon as* the PTAB enters a final written decision" and that its "effect is not delayed pending completion of an appeal to the Federal Circuit" (emphasis added)).

The statute provides that preclusion will arise upon issuance of a "final written decision under section 318(a)." 35 U.S.C. § 315(e)(2). Section 318(a), in turn, provides that the Board shall "issue a final written decision" in any instituted

IPR. Neither provision refers to appealability. Whether a request for rehearing makes a final written decision temporarily non-appealable makes no difference; the statutory trigger is issuance of a "final written decision," not an appealable final written decision or final agency action.

The distinction between finality for preclusion purposes and appealability is a familiar one. For example, the pendency of post-trial motions does not make a district court decision "non-final" for preclusion purposes or prevent it from having preclusive effect, even if the motions make it unappealable. *See Tripati v. Henman*, 857 F.2d 1366, 1367 (9th Cir. 1988) (per curiam) ("A pending Rule 59(e) motion similarly does not deprive a judgment of finality for *res judicata* purposes."); *Perez v. Volvo Car Corp.*, 247 F.3d 303, 309-10 n.4 (1st Cir. 2001) (same); 18 James Wm. Moore, *Moore's Federal Practice* § 131.30[2][c][iv], at 131-100 (3d ed. 1998) ("Finality should attach for claim preclusion purposes at the time of entry of judgment … while such a [post-trial] motion is pending the judgment is unappealable even though it has preclusive effect."); *see also* Fed. R. Civ. P. 60. Indeed, the distinction is reflected in the Board's own practice. The Board applies § 315(e)(1), the sister provision to § 315(e)(2) that bars re-litigation of invalidity grounds in subsequent Patent Office proceedings, even where a rehearing request is pending in the first proceeding. *Apple Inc. v. Personalized Media Commc'ns LLC*, IPR2016-01520, 2018 WL 922376, at *2 (P.T.A.B. Feb.

15, 2018). The operative language is the same in the two provisions, and it should be applied consistently.

The Board's denials of Janssen's rehearing requests—which are styled "Decisions Denying Patent Owner's Request for Rehearing," *not* new "Final Written Decisions"—confirm that the "final written decision[s] under section 318(a)," 35 U.S.C. § 315(e)(2), were those issued prior to trial in the district court.[5]

C. The District Court's Judgment Should Be Reversed, and Judgment Should Be Entered for Janssen.

Because the only basis for the district court's judgment in favor of Defendants was barred by § 315(e)(2), this Court should reverse and direct entry of judgment for Janssen. The district court has already rejected Defendants' § 112 defenses and concluded that their ANDAs would induce and contribute to infringement; there are no other defenses remaining; and there is no cross-appeal. Appx74, Appx102, Appx123, Appx142. Therefore, the district court should enter judgment and issue an appropriate injunction under § 271(e)(4).

III. In the Alternative, the District Court's Ruling on the Merits of Defendants' Obviousness Defenses Should Be Reversed.

The combination therapy of the '438 patent revolutionized the treatment of advanced prostate cancer, achieved enormous commercial success, and produced

[5] In any event, now that the Board has denied rehearing, the "Final Written Decisions" are indisputably appealable. Thus, Defendants may not "assert" their obviousness defenses in this ongoing "civil action." 35 U.S.C. § 315(e)(2).

results contrary to the expectations in the art at the time of invention. But in assessing obviousness, the district court erred from the outset by simply assuming that a skilled artisan would pursue a cancer therapy that involved abiraterone, and it compounded the error by failing to engage in any distinct analysis of reasonable expectation of success. And although a proper analysis of the objective evidence of non-obviousness might have avoided the hindsight trap into which the court fell, the court erred again by applying the wrong framework for assessing such evidence. The result is a decision premised on legal error that should be reversed.

A. The District Court Erroneously Assumed that a Skilled Artisan Would Have Selected Abiraterone for Development.

The court's threshold error was its failure to analyze whether there was any reason a skilled practitioner would have pursued development of a therapy that included abiraterone based on the state of the art in 2006. *See Cyclobenzaprine*, 676 F.3d at 1072 ("Evidence of obviousness … is insufficient unless it indicates that … skilled artisans would have had a reason to select the route that produced the claimed invention."). In other words, the court never identified any reason for "pluck[ing] one reference out of the sea of prior art" for further development or modification. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016); *see also Polaris Indus.*, 882 F.3d at 1069 n.4; *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1303-04 (Fed. Cir. 2010) ("it is not enough to simply show that the [prior art] references disclose the

claim limitation"; it is "important to identify a reason" to pursue it). Instead, the court essentially gave Defendants a pass on establishing this critical foundational step. This is legal error.

Had the court addressed the question, it could not have made the findings required to establish obviousness. A skilled artisan would not have chosen to pursue an anti-cancer therapy using abiraterone in 2006, because abiraterone was in a class of compounds widely regarded as not worth pursuing at that time.

Indeed, as the court itself found, the "prevailing belief" at the time of invention "was that, once [prostate] cancer resumed growing after ADT, the cancer became androgen independent." Appx87. Despite numerous attempts, no secondary hormonal therapy had ever shown a survival benefit or received FDA approval for prostate cancer. Appx22465, Appx22552-22553, Appx22764-22765. As noted above, the terminology used to describe advanced prostate cancer (such as "androgen-independent" or "hormone resistant") reflected this reality, Appx21014-21015, Appx22764, Appx23182, Appx28524, Appx23215, Appx27880, including in articles by Defendants' oncology expert, Appx22576-22577, and researchers considered secondary hormonal therapies "antiquated," Appx21140-21141, Appx22176-22177; Appx28524 (advising to avoid "futile hormonal manipulations"). At the time, over 200 compounds for the treatment of advanced prostate cancer were in development, Appx28488, and a 2005 paper

surveying the "most promising agents in clinical development" did not even mention abiraterone—or any other secondary hormonal drug. Appx28560-28570, Appx22769-22770.

To be sure, the district court did conclude that "abiraterone had been identified in the prior art as a second-line prostate cancer treatment." Appx115. But the court did not consider whether, much less explain *why*, a skilled artisan would have chosen to pursue abiraterone over the hundreds of other, more-promising alternatives identified at the time. At most, the court held that the existence of "other anti-cancer agents, perhaps even more promising ones," fell short of teaching away from abiraterone because it suggested only that abiraterone was not the "'preferred, or most desirable'" option. Appx117 (quoting *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004)). But teaching away is not the issue: the issue is whether a skilled artisan would have been motivated to select abiraterone for development in the first place. And even if teaching away were the issue, the prevailing view in 2006—which saw second-line hormonal therapies as "antiquated" or "futile"—plainly "criticize[d], discredit[ed], or otherwise discourage[d]" the development of abiraterone. *Fulton*, 391 F.3d at 1201.[6]

[6] The court's reliance on earlier references—the 1994 Barrie article and the 2004 O'Donnell paper (based on the 1999 Phase I study)—does not fix this problem. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed. Cir. 2013) ("considerable time lapse" between prior art and invention shows "a resort to

B. The District Court's Conclusions Regarding Reasonable Expectation of Success Rest on Legal Error.

Although the district court, unlike the Board, properly construed the claims to require that *both* the abiraterone *and* the prednisone have an anti-cancer effect, Appx4081 (construing "treating"), it made the same error as the Board on "reasonable expectation of success": it failed to consider whether a skilled artisan would have had a reasonable expectation of success in achieving the invention *as claimed*. The court made no finding that a skilled artisan—even one motivated to make the combination—would have expected both drugs to have an anti-cancer effect in a combination therapy. That was a legal error. *Intelligent Bio-Sys.*, 821 F.3d at 1367 ("[F]ailure to consider the appropriate scope of the … patent's *claimed invention* in evaluating the reasonable expectation of success … constitutes a legal error.").

Moreover, the record would not have supported such a finding, much less by clear and convincing evidence. Indeed, there was no evidence to support a finding that *either* drug, on its own, would be expected to provide "treatment"—*i.e.*, "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," Appx3599—in 2006.

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hindsight"). By 2006, the prevailing view, as noted, was that secondary hormonal therapies were not worth pursuing.

As noted above, those in the field did not view second-line hormonal therapies, such as abiraterone, as promising. The O'Donnell 2004 paper was not enough to change that prevailing view because the late-1990s studies it reported were not designed to measure anti-cancer effects. Indeed, Boehringer—one of the largest pharmaceutical companies in the world, which had every incentive to develop a drug that could be profitable in a market with no good alternative—abandoned abiraterone shortly after those studies, which it had sponsored, ended. Appx21022, Appx21144-21145, Appx22887. And numerous other pharmaceutical companies passed on licensing abiraterone between 1999 and 2004 before a small smart-up took a chance on it. Appx21022, Appx21025-21026, Appx21145-21147, Appx22887-22888.

And there is even less evidence to suggest that skilled artisans in 2006 would have expected prednisone to provide "treatment" as the district court understood that term. Defendants' own oncology expert testified that Sartor 1998—the primary reference the court cited—does *not* show that prednisone treats prostate cancer and that he "do[es] not recall ever feeling that there was any proven anti-cancer benefit from prednisone." Appx22169-22170. He further conceded that "physicians [he] was in contact with also didn't have a sense that there was any proven anti-cancer benefit" from prednisone. Appx22170. And, by 2006, there were even "more data that [prednisone] doesn't treat mCRPC." Appx22843-

22844, Appx22845-22848 (further studies "confirmed a lack of impact on survival of glucocorticoids for mCRPC"), Appx28705 (2006 reference explaining that "no study with these agents has demonstrated a survival advantage"); *see also Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985) (inquiry is "at the time the invention was made" and "the state of the art that existed at the time").

Moreover, even if the prior art had provided a basis for a skilled artisan to expect that abiraterone and prednisone would each "treat" cancer on its own, there was no evidence—and certainly not clear and convincing evidence—to cause a skilled artisan to expect *both* elements to have an anti-cancer effect in combination. Indeed, the undisputed evidence showed that two agents can work at cross purposes. Appx21574, Appx22895, Appx22334. And the sole reference relied on by Defendants at trial for combining abiraterone and prednisone because of alleged anti-cancer effects, Vidal 2004, provides no reason to expect either element (let alone both) to be effective. Vidal, in fact, suggests that hormone-resistant prostate cancer is androgen-independent and thus not likely to respond to a further reduction in androgens (such as with abiraterone), as Defendants' expert conceded. Appx22649-22652. What is more, Vidal suggests avoiding glucocorticoids (like prednisone), because they might make the cancer worse. Defendants' expert

disparaged this as a mere "hypothesis," but did not dispute that Vidal teaches away. Appx22645-22649.

Ultimately, the court did not point to Vidal or anything else to support a finding that a person of ordinary skill would have expected each element of the claimed combination to have an anti-cancer effect. Instead, it simply failed to make the requisite finding. *See Intelligent Bio-Sys.*, 821 F.3d at 1367. This legal error warrants vacatur.

C. The District Court's Evaluation of the Objective Indicia Was Plagued by Legal Errors.

Objective indicia are often "the most probative and cogent evidence in the record" on the issue of obviousness, *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 769 F.3d 1339, 1343 (Fed. Cir. 2014) (en banc) (per curiam), and they "must always when present be considered," *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 837 (Fed. Cir. 2015). This Court has held that a district court commits reversible error "by making its finding that the patents in suit were obvious before it considered the objective considerations and by shifting the burden of persuasion to" the patentee. *Cyclobenzaprine*, 676 F.3d at 1075.

The district court did precisely that. Rather than considering objective indicia as part of a comprehensive obviousness analysis, the court reached a conclusion on obviousness and only then turned to "objective considerations presented by plaintiffs," holding that these considerations did "not alter [its]

conclusion." Appx118; *see also* Appx118 (citing *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 719 (Fed. Cir. 1991), for the proposition that "secondary considerations did not carry sufficient weight to *override* obviousness determination based on primary considerations" (emphasis added)). *Cyclobenzaprine* teaches that courts should not reach a "conclusion" to be "alter[ed]" by the objective evidence, and they certainly should not shift the burden to the patentee to "override" an obviousness determination with secondary considerations. *See also Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1534 (Fed. Cir. 1983) (burden of persuasion never shifts to patentee).

The court's improper burden-shifting also permeates its treatment of individual objective indicia. Consider commercial success. The administration of ZYTIGA according to its label (*i.e.*, in combination with prednisone to treat cancer) is the commercial embodiment of the claimed invention—a fact that was necessary to the court's now-undisputed infringement determination. Appx132 ("I find that the combination therapy embodied in the label meets the claim limitations of the patent."). And there is no dispute that ZYTIGA as labeled has been a huge commercial success, generating "billions of dollars in sales." Appx118. When, as here, a patentee presents evidence of the tie between the patented invention and objective indicia, such as commercial success, there is a "presumption of nexus."

WBIP, 829 F.3d at 1329. It was therefore Defendants' burden to show that ZYTIGA's success was attributable to something *other than* the claimed invention.

But when Defendants relied on argument—not evidence—to assert that the success was attributable to abiraterone alone, the court shifted the burden to Janssen, ultimately finding Janssen's evidence "suggestive though not conclusive." Appx118. This was error: nexus is presumed in the absence of contrary evidence. It was also inconsistent with the court's finding that "[a]biraterone monotherapy is an off-label use, and there is no evidence in the record that this proposed off-label use is or would be 'substantial.'" Appx141.

Similarly, when Janssen presented undisputed evidence that the asserted "blocking patent" was available for license—indeed, it was actively shopped to major pharmaceutical companies without success, Appx120, Appx21145-21146—the court should have required *Defendants* to show that the patent actually presented an obstacle to those in the field. *See Acorda*, 903 F.3d at 1338 ("the mere existence or sheer number of blocking patents does not, without more, 'necessarily detract from evidence of commercial success of a product or process'"). Instead, the court simply presumed a deterrent effect and concluded that BTG's licensing efforts failed to satisfy some previously unknown standard of enthusiasm and "appear to have been lackluster" and "desultory." Appx120. The court's presumption and standard have no support in the law. Moreover,

regardless of whether BTG was an enthusiastic licensor—and it certainly was—Defendants presented no evidence that a company interested in developing a therapy that included abiraterone would have been unable to obtain a license or even discouraged by the existence of a prior patent.[7] It was Defendants' burden to do so.

The court committed a similar error with respect to skepticism. The evidence of skepticism was extensive, Appx22774-22776, Appx22832, Appx22844-22845, Appx22899-22900, Appx22554, Appx22649-22650, Appx21140-21142, Appx21156-21157, Appx21017-21019, Appx27876-27879, Appx23183, Appx28524, Appx28705, and the court itself found that "the prevailing belief was that" mCRPC was "androgen independent." Appx87. This prevailing belief necessarily means—as the evidence showed—that there was skepticism toward second-line hormonal therapies. The claimed combination is a second-line hormonal therapy, so nexus is presumed. *See WBIP*, 829 F.3d at 1329. Yet the district court surmised that the "skepticism seems to be directed to abiraterone itself, rather than the claimed combination," Appx121, and turned to Janssen to disprove that proposition. This was both illogical and legally wrong.

[7] Beyond the fact that the patent had been licensed to Boehringer, which abandoned its efforts, it is undisputed that BTG repeatedly tried to license the patent, including to major pharmaceutical companies like Bristol-Myers Squibb, U.S. BioScience, and Wyeth. *See* Appx120, Appx21145-21146.

As the Board did, the court failed to explain how skepticism toward "abiraterone itself" was not also skepticism toward a combination therapy that included abiraterone, and it erred by imposing the burden on Janssen to rebut its unsupported assumption that it was not.

The court committed even more fundamental errors in its approach to long-felt need and unexpected results. As the court acknowledged, Janssen introduced evidence that ZYTIGA plus prednisone "had less toxicity, was better tolerated, and improved overall survival" compared to existing mCRPC therapies, the chemotherapy drugs Taxotere and Jevtana. Appx122. The FDA's priority review approvals confirm that the claimed invention, as embodied in ZYTIGA plus prednisone, was not merely safe and effective, but a substantial improvement over then-available alternatives. *See Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006). The court, however, gave little weight to this evidence because it viewed the improvement in overall survival, from 2.5 months with chemotherapy to 4 months with ZYTIGA plus prednisone, as "incremental" and a difference "'merely in degree,'" not "'in kind.'" Appx122 (citation omitted).

This analysis was flawed in at least two respects.

First, under this Court's precedent, a mere difference in degree is something "within the capabilities of one skilled in the art." *In re Huang*, 100 F.3d 135, 139

(Fed. Cir. 1996); *see also Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013). There was no evidence that improving survival rates by 60 percent was a matter of routine tweaks. *See Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1274 (Fed. Cir. 2018) (finding clear error where a district court discounted a 66% improvement in bioavailability as a difference in degree, not kind).

Second, the court ignored other ways ZYTIGA plus prednisone improved upon chemotherapy, most importantly the combination therapy's undisputed greater tolerability and ease of administration. Indeed, chemotherapy's toxicity meant that many mCRPC patients could not—or chose not to—receive it. Appx22282-22283, Appx21989-21990. For such patients, ZYTIGA plus prednisone increased survival from *zero* months to 4 months or more—undoubtedly a difference in kind. Moreover, the therapy's improvement in overall quality of life undisputedly "changed the standard of care" in this field. Appx21103-21104, Appx21576-21577 (invention "was practice changing").

Given the practice-changing nature of this unexpected and commercially successful combination therapy, proper consideration of the objective indicia would have protected against hindsight bias and would have led the court to appreciate the non-obviousness of the claimed inventions.

CONCLUSION

The Court should vacate the Board decisions and remand for further proceedings. The Court should reverse the district court's judgments and direct entry of judgment for Janssen, or, alternatively, vacate the judgments of invalidity and remand for further proceedings.

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Respectfully submitted,

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