19-1147, 19-1148, 19-1323, 19-1324, 19-1325

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

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

Plaintiffs-Appellants

v.

AMERIGEN PHARMACEUTICALS, INC., AMERIGEN PHARMACEUTICALS LIMITED,

Defendants-Appellees

JANSSEN ONCOLOGY, INC.,

Appellant

v.

AMERIGEN PHARMACEUTICALS LIMITED, ARGENTUM PHARMACEUTICALS, LLC,

Appellees

[caption continued on inside cover]

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

JANSSEN ONCOLOGY, INC.,

Appellant

v.

WOCKHARDT BIO AG,

Appellee

Appeals from the United States District Court for the District of New Jersey in case nos. 2:15-cv-05909-KM-JBC, 2:16-cv-02449-KM-JBC, 2:17-cv-06435-KM-JBC, Judge Kevin McNulty, and from the Patent Trial and Appeal Board in IPR2016-00286, IPR2016-01317, IPR2016-01332, and IPR2016-01582, and IPR2017-00853

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The names of the real parties in interest represented by me (not including parent corporations and publicly held stockholders) are:

None other than those listed above

The parent corporations and publicly held companies that own 10% or more of stock in the parties represented by me are:

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

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BTG Int'l Ltd. v. Amerigen Pharm., Inc., No. 2:16-cv-02449-KM-JBC (D.N.J.);

BTG Int'l Ltd. v. MSN Pharm. Inc., No. 2:18-cv-02372-KM-JBC (D.N.J.);

Janssen Biotech, Inc. v. Mylan Pharm., Inc., No. 1:15-cv-00130-IMK (N.D.W. Va.);

BTG Int'l Ltd. v. Qilu Pharm. Co., No. 2:18-cv-16521-KM-JBC (D.N.J.).

Dated: February 15, 2019 /s/Dan L. Bagatell

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None other than those listed above

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BTG Int'l Ltd. v. Amerigen Pharm., Inc., No. 2:16-cv-02449-KM-JBC (D.N.J.);

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Janssen Biotech, Inc. v. Mylan Pharm., Inc., No. 1:15-cv-00130-IMK (N.D.W. Va.);

BTG Int'l Ltd. v. Qilu Pharm. Co., No. 2:18-cv-16521-KM-JBC (D.N.J.).

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Janssen Biotech, Inc. v. Mylan Pharm., Inc., No. 1:15-cv-00130-IMK (N.D.W. Va.);

BTG Int'l Ltd. v. Qilu Pharm. Co., No. 2:18-cv-16521-KM-JBC (D.N.J.).

Dated: February 15, 2019 /s/Teresa Stanek Rea

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TABLE OF ABBREVIATIONS AND CONVENTIONS

abiraterone	abiraterone acetate
AIA	Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (effective September 16, 2012)
ANDA	Abbreviated New Drug Application
Appellees	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., Amerigen Pharmaceuticals, Inc., Amerigen Pharmaceuticals Limited, and Argentum Pharmaceuticals LLC
Attard	Gerhardt Attard et al., *Selective Blockade of Androgenic Steroid Synthesis by Novel Lyase Inhibitors as a Therapeutic Strategy for Treating Metastatic Prostate Cancer*, 96 BJU Int'l 1241 (2005) (Appx27910-27915)
Barrie	S.E. Barrie et al., *Pharmacology of Novel Steroidal Inhibitors of Cytochrome* P$450_{17\alpha}$ *(17α-Hydroxylase/C17-20 Lyase)*, 50 J. Steroid Biochem. Molec. Biol. 267 (1994) (Appx23056-23062)
Barrie patent	U.S. Patent 5,604,213 to Susan E. Barrie et al. (Appx27737-27755)
Fakih	Marwan Fakih et al., *Glucocorticoids and Treatment of Prostate Cancer: A Preclinical and Clinical Review*, 60 Urology 553 (2002) (Appx23136-23144)
Fosså	S.D. Fosså et al., *Flutamide Versus Prednisone in Patients with Prostate Cancer Symptomatically Progressing After Androgen Ablative Therapy: A Phase III Study of the European Organization for Research and Treatment of Cancer Genitourinary Group*, 19 J. Clin. Oncol. 62 (2001) (Appx27786-27797)
FDA	Food and Drug Administration

Garnick	Marc B. Garnick et al., *Androgen Deprivation Therapy, the Future*, *in* Prostate Cancer Principles and Practice (2006) (Appx23207-23225)
Gerber	Glenn S. Gerber et al., *Prostate Specific Antigen for Assessing Response to Ketoconazole and Prednisone in Patients with Hormone Refractory Metastatic Prostate Cancer*, 144 J. Urology 1177 (1990) (Appx23053-23055)
Harris	Katherine A. Harris et al., *Low Dose Ketoconazole with Replacement Doses of Hydrocortisone in Patients with Progressive Androgen Independent Prostate Cancer*, 168 J. Urology 542 (2002) (Appx27829-27832)
IPR	*inter partes* review
the IPRs	the *inter partes* reviews in IPR2016-00286, IPR2016-01332, and IPR2016-01582
Janssen	Appellants BTG International Ltd., Janssen Biotech, Inc., Janssen Oncology, Inc., and Janssen Research & Development, LLC
Jarman	Michael Jarman et al., *The 16,17-Double Bond Is Needed for Irreversible Inhibition of Human Cytochrome P450$_{17\alpha}$ by Abiraterone (17-(3-Pyridyl)adrosta-5,16-dien-3β-ol) and Related Steroidal Inhibitors*, 41 J. Med. Chem. 5375 (1998) (Appx23078-23086)
mCRPC	metastatic castration-resistant prostate cancer
O'Donnell	A. O'Donnell et al., *Hormonal Impact of the 17a-Hydroxylase/C$_{17,20}$-lyase Inhibitor Abiraterone Acetate (CB7630) in Patients with Prostate Cancer*, 90 Br. J. Cancer 2317 (2004) (Appx23171-23179)
POSA	person of ordinary skill in the art
Potter	Gerald A. Potter et al., *Novel Steroidal Inhibitors of Human Cytochrome P450$_{17\alpha}$ (17α-Hydroxylase-C$_{17,20}$-lyase): Potential Agents for the Treatment of Prostatic Cancer*, 38 J. Med. Chem. 2463 (1995) (Appx27728-27736)
PSA	prostate-specific antigen

PTAB or Board	Patent Trial and Appeal Board
PTO	United States Patent and Trademark Office
Sartor	Oliver Sartor et al., *Effect of Prednisone on Prostate-Specific Antigen in Patients with Hormone-Refractory Prostate Cancer*, 52 Urology 252 (1998) (Appx23087-23091)
Sartor 2006	Oliver Sartor, *The Continuing Challenge of Hormone-Refractory Prostate Cancer*, Clin. Genitourinary Cancer 238 (2006) (Appx28705-28706)
Tannock	Ian F. Tannock et al., *Chemotherapy with Mitoxantrone Plus Prednisone or Prednisone Alone for Symptomatic Hormone-Resistant Prostate Cancer: A Canadian Randomized Trial with Palliative End Points*, 14 J. Clin. Oncology 1756 (1996) (Appx23063-23073)
Vidal	L. Vidal et al., *Reversing Resistance to Targeted Therapy*, 16 J. Chemotherapy 7 (2004) (Appx23181-23187)
(*x*:*y*-*z*)	column *x*, lines *y* through *z*
’438 patent	U.S. Patent No. 8,822,438 (Appx755-766)

RELATED CASES

No other appeals involving this case have been before this or any other appellate court. The decision in this case may affect the following pending district court cases:

- *BTG Int'l Ltd. v. Amerigen Pharm., Inc.*, No. 2:16-cv-02449-KM-JBC (D.N.J.);
- *BTG Int'l Ltd. v. MSN Pharm. Inc.*, No. 2:18-cv-02372-KM-JBC (D.N.J.);
- *Janssen Biotech, Inc. v. Mylan Pharm., Inc.*, No. 1:15-cv-00130-IMK (N.D.W. Va.);
- *BTG Int'l Ltd. v. Qilu Pharm. Co.*, No. 2:18-cv-16521 (D.N.J.).

INTRODUCTION

Janssen's '438 patent claims methods of treating prostate cancer by administering two prior-art drugs. The first, abiraterone, was known as a potent, selective inhibitor of CYP17, a key enzyme for synthesizing androgens that promote prostate-cancer growth. The second, prednisone, was a steroid used to counter adverse side effects of CYP17 inhibitors and to ease discomfort in prostate-cancer patients. Research also suggested that prednisone had anti-cancer effects of its own.

Appellees presented a straightforward obviousness case to the PTAB and the district court, and after four trials, six judges all agreed that the claims were obvious. On appeal, Janssen argues that all those determinations were wrong, but Janssen's arguments are mistaken at every turn.

Janssen first contends that the PTAB misconstrued the claims by not requiring prednisone to have an independent anti-cancer effect. But Janssen waived that argument by not seeking that construction, and in any event the Board properly concluded that the broadest reasonable construction of "treating" prostate cancer with prednisone includes using prednisone for palliation or making abiraterone more tolerable by offsetting its side effects. Affirmance of that construction would fully dispose of this case. Moreover, substantial evidence supported the findings underlying the Board's obviousness conclusion under either construction.

Janssen also disputes the district court's separate obviousness determination, but this Court need not reach any district-court issues if it affirms in any of the IPR appeals, and Janssen's complaints have no merit anyway. Janssen presents a smorgasbord of challenges to the district court's obviousness analysis, but the disputes were fundamentally factual, and Janssen comes nowhere close to overcoming the deferential clear-error standard of review. To avoid the district court's reasoning altogether, Janssen argues that 35 U.S.C. § 315(e)(2) estopped Appellees from arguing obviousness in the district court once the PTAB found the claims obvious. But that statutory form of collateral estoppel did not apply because (a) the statute does not bar *prevailing* IPR petitioners from maintaining invalidity defenses in district court and (b) the PTAB's decisions were on rehearing and thus not final when the district court ruled.

This Court should affirm that the claimed invention was obvious.

STATEMENT OF ISSUES

1. Did Janssen waive its argument that the PTAB erred in its claim construction by agreeing to that construction?

2. Did the PTAB properly apply the broadest-reasonable-construction standard in concluding that "treating" prostate cancer with prednisone is not limited to attacking the cancer itself and can include reducing side effects of co-administered abiraterone and reducing patient discomfort?

3. Did substantial evidence support the PTAB's determination that Janssen's claims were unpatentable under either construction of "treating"?

4. Did the district court reasonably weigh the evidence in making the factual findings underlying its conclusion that the claimed invention was obvious?

5. Did the district court correctly conclude that Appellees were not collaterally estopped under § 315(e)(2) from presenting their obviousness defense at trial when (a) Appellees had won, rather than lost, before the PTAB, and (b) the PTAB's decisions were on rehearing and thus not final?

6. Did the district court err in finding that Appellees would indirectly infringe if the claims were valid when FDA never approved using prednisone for anti-cancer effects and the district court never found the prerequisite direct infringement?

STATEMENT OF THE CASE

I. Statement of Facts

A. Abiraterone and other CYP17 inhibitors were known to inhibit production of androgen hormones important for prostate-cancer growth

Long before the '438 patent's 2006 priority date, scientists understood that androgen hormones such as testosterone promote prostate-cancer growth. Appx758 ('438(1:49-51)); Appx27739(1:10-15) (Barrie patent). Therapies aimed at suppressing androgen production were thus a mainstay of prostate-cancer treatment. Appx758 ('438(1:44-56)); Appx23171-23172 (O'Donnell). Surgical or chemical

castration provided a "first-line" treatment by eliminating most androgen production, but residual androgen produced by adrenal glands could eventually support cancer growth. Appx23171 (O'Donnell); Appx27910-21911 (Attard).

CYP17 (17α-hydroxylase/$C_{17,20}$-lyase) is a key enzyme for both testicular and adrenal synthesis of androgens. Appx27911 (Attard). By the 1990s, researchers understood that abiraterone and ketoconazole are CYP17 inhibitors that effectively suppress both testicular and adrenal androgen production. Appx27739(1:10-39) (Barrie patent); Appx23172 (O'Donnell). Researchers had studied and used both abiraterone and ketoconazole for treating prostate cancer. Appx760 ('438(5:22-29)) (CYP17 inhibitors "ha[d] been shown to be useful in the treatment of cancer," specifically "androgen-dependent … disorders like prostate cancer"); Appx27739(1:10-15) (Barrie patent discussing abiraterone); Appx23171-23178 (O'Donnell discussing abiraterone); Appx23053-23055 (Gerber); *see also* Appx23213-23124 (Garnick) (abiraterone demonstrated selective CYP17-inhibition "resulting in inhibition of testosterone production in both the adrenals and the testes").

Abiraterone was considered especially selective and potent. Appx23171-23178 (O'Donnell); Appx27912 (Attard). Studies had shown that it suppressed androgen levels in castrate and non-castrate patients with advanced prostate cancer, and it had been identified as a promising "second-line" treatment for "refractory" prostate cancer that did not respond to other treatments. Appx23178 (O'Donnell).

B. Prednisone and other glucocorticoids were known to reduce prostate-cancer patients' discomfort and to counteract side effects of androgen inhibitors

Glucocorticoids are steroid hormones produced in the adrenal glands that have wide-ranging physiological effects and numerous clinical applications. Synthetic glucocorticoids such as prednisone have been used for palliative effects in treating refractory prostate cancer since the 1950s. Appx23087 (Sartor).

Because CYP17 inhibitors also suppress synthesis of beneficial adrenal hormones, researchers understood that treatment with CYP17 inhibitors could "necessitate concomitant administration of replacement glucocorticoid." Appx23171 (O'Donnell). A 1990 study evaluating ketoconazole treatment for refractory prostate cancer employed a combination therapy that included prednisone as a replacement glucocorticoid. Appx23053-23055 (Gerber). Another prior-art study found abnormal adrenal function in prostate cancer patients receiving abiraterone, observed the "common practice" of administering supplementary glucocorticoids during ketoconazole treatment, and called for study of whether abiraterone similarly required concurrent glucocorticoid administration. Appx23177 (O'Donnell); *see also* Appx23214 (Garnick) ("Adrenocortical suppression may necessitate concomitant treatment with replacement glucocorticoid" when administering abiraterone to prostate-cancer patients.).

Beyond palliation and offsetting adrenal suppression, the prior art described independent therapeutic benefits of administering prednisone to patients with refractory prostate cancer. A 1998 study found that treatment with prednisone alone reduced levels of prostate-specific antigen (PSA), indicating anti-prostate-cancer activity, and improved symptoms in many refractory-prostate-cancer patients. Appx23087-23091 (Sartor).

C. The ’438 patent claims co-administering abiraterone and prednisone to treat prostate cancer

Janssen acquired two patents involving abiraterone and its use in treating prostate cancer. The Barrie patent, which issued in 1997 and expired in 2016, covered abiraterone and using abiraterone to treat prostate and other cancers. Appx27737. This case involves the ’438 patent, which claims priority to a 2006 provisional application. Appx755.

The ’438 specification describes treating various types of cancer by co-administering a CYP17 inhibitor with “at least one additional therapeutic agent such as an anti-cancer agent or a steroid.” Appx755-762 (’438(Abstract, 1:5-16, 2:9-16, 3:12-20, 5:9-17, 10:53-56)). Among myriad other combinations, the specification states that abiraterone may be administered with a glucocorticoid steroid such as prednisone. Appx758-762 (’438(1:12-16, 5:9-17, 10:15-21)).

During prosecution, Janssen narrowed the claims to using abiraterone with prednisone to treat prostate cancer. Claim 1 recites:

> 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 ('438(16:16-20)).[1]

The examiner repeatedly rejected the claims as obvious over the 2004 O'Donnell article, which taught that abiraterone is a safe, effective, and selective CYP17 inhibitor and discussed co-administering a glucocorticoid with abiraterone, and the 1996 Tannock article, which taught co-administering prednisone with an anti-cancer drug when treating refractory hormone-resistant prostate cancer. *E.g.*, Appx25938-25942; Appx25983-25989; Appx26023-26029. The examiner maintained that rejection over Janssen's attempted distinctions and claims of unexpected results. *E.g.*, Appx25983-25989; Appx26023-26029. The claims were ultimately allowed, however, based on Janssen's assertion that its FDA-approved abiraterone product, Zytiga®, had enjoyed commercial success. Appx26112-26114; Appx26505-26507. The notice of allowance did not recognize that Zytiga consists of abiraterone without prednisone and that Janssen owned the blocking patent on using abiraterone.

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[1] Janssen's Statement touts hypotheses and later studies by Johann de Bono. The specification describes none of that, however, and the patent as issued did not name de Bono as an inventor.

Janssen also presents an exaggerated story of skepticism and unexpected results. Appellees will discuss those issues below. For now, suffice it to say that the facts were disputed, and the PTAB and district court rejected Janssen's account.

II. Procedural History

After various companies sought FDA approval to market generic versions of Zytiga with labels mentioning co-administration with prednisone, Janssen sued for patent infringement. The district court consolidated the cases.

Several sets of defendants (Appellees here) filed IPR petitions asserting that all claims of the '438 patent were unpatentable for obviousness. The PTAB conducted three separate reviews. In the first (*Amerigen*) and second (*Mylan*), the petitioners asserted that the claims were unpatentable over O'Donnell, which taught that abiraterone is a potent, selective CYP17 inhibitor that might be best administered with a glucocorticoid to treat prostate cancer, and the Gerber patent, which taught administering ketoconazole with prednisone to treat refractory metastatic prostate cancer. The petitioners alternatively asserted obviousness over Barrie's patent on abiraterone plus Gerber. Appx29276-29348; Appx35051-35125. In the third (*Wockhardt*) review, the petitioner contended that the claims were obvious over Gerber, O'Donnell, and Sartor's 1998 article describing prednisone's independent ability to reduce PSA levels in refractory-prostate-cancer patients. Appx41321-41400.

The district court and the PTAB ultimately reached the same result, issuing four separate decisions finding all claims invalid or unpatentable for obviousness.

A. In three parallel IPRs, the PTAB found all claims unpatentable for obviousness

In January 2018, the PTAB issued three separate merits decisions.

1. In the *Amerigen* IPR, the PTAB concluded that the claims were obvious over both O'Donnell + Gerber and Barrie + Gerber. Appx178-225.

At institution, the Board adopted the patentees' lexicography and interpreted "a therapeutically effective amount of prednisone" as "an amount of prednisone effective for treating prostate cancer," and "treating" as "includ[ing] 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." Appx156-158. Janssen did not dispute those constructions in its patent-owner response, Appx29550, and the Board maintained them, Appx184-185.

Turning to the prior art, the Board rejected Janssen's argument that POSAs considered teachings about ketoconazole irrelevant to abiraterone and rejected Janssen's related suggestion that POSAs were unmotivated to combine abiraterone with a glucocorticoid. The Board also found that prior art did not discourage treating prostate-cancer patients with prednisone, and it rejected Janssen's attempt to discredit Gerber. Appx192-204.

The Board further found that POSAs reasonably expected success using prednisone in a therapy for metastatic prostate cancer. The Board noted that the '438 specification described administering abiraterone with "at least one additional therapeutic agent, *such as an anti-cancer agent or a steroid*." Appx205. It further observed that the specification defined prednisone as both an "anti-cancer agent" (as

an antibiotic) and a steroid (a glucocorticoid). The specification thus contemplated that prednisone and other steroids may have therapeutic effects apart from anti-cancer effects, and its statement that "treating" "includes" anti-cancer effects did not exclude other benefits of co-administration such as palliation. Appx205-208.

The Board found only weak objective evidence of non-obviousness. Some researchers were skeptical of abiraterone as a stand-alone treatment, but others were not, and the skepticism was not aimed at the claimed combination. The Board found little evidence of unexpected results and no long-felt need for the claimed combination treatment. Finally, the Board found that although Zytiga had some commercial success, the blocking patent on abiraterone deterred research by others, and the Board was unpersuaded that Zytiga's commercial success was due to the claimed combination rather than abiraterone itself. Appx210-219.

2. The Board's reasoning in the *Mylan* IPR was similar. Appx248-297.

3. The *Wockhardt* IPR addressed obviousness over a different combination: Gerber, O'Donnell, and Sartor. Sartor reported that administration of prednisone alone reduced PSA levels in patients with hormone-refractory prostate cancer. Wockhardt thus contended that prednisone was expected to have its own anti-cancer effects in addition to providing palliation and reducing adverse side effects of CYP17 inhibitors. The PTAB instituted review, Appx313-316, and found the claims obvious, Appx327-377.

In its response, Janssen again did not dispute the Board's claim constructions. *See* Appx41639-41640; Appx332-334. Janssen did dispute that Gerber taught co-administering ketoconazole and prednisone to treat prostate cancer, but the Board found that O'Donnell confirmed that teaching. Appx339-341. The Board also rejected Janssen's attack on O'Donnell and concluded that POSAs would have considered ketoconazole and abiraterone to be similar CYP17 inhibitors. Appx341-343. The Board further found that O'Donnell encouraged study of co-administering a glucocorticoid with abiraterone to reduce side effects of CYP17 inhibitors. Appx343-349. It also found that Sartor taught that (a) prednisone was likely to have its own anti-prostate-cancer effects in addition to ameliorating side effects of other drugs, (b) studies of non-CYP17 inhibitor treatments did not discourage study of the claimed invention, and (c) POSAs reasonably expected that the claimed invention would succeed *regardless* of whether "treating" prostate cancer was defined as limited to anti-cancer effects. Appx349-359. The panel again found that Janssen's objective evidence of non-obviousness was weak and did not outweigh the countervailing evidence on the other *Graham* factors. Appx360-371.

Janssen requested rehearing in each IPR in February 2018, raising various factual issues. Appx30135-30151; Appx35725-35741; Appx41973-41988.

B. The district court also found the claims invalid for obviousness

While Janssen's rehearing requests remained pending, the district-court action proceeded through trial.

Shortly after the January 2018 rulings, Janssen filed a motion *in limine* asking the district court to preclude Appellees from raising their obviousness defenses at trial. Appx13128-13152. Janssen argued that 35 U.S.C. § 315(e)(2) estopped Appellees from asserting obviousness at trial even though Appellees had prevailed in the IPRs and even though Janssen conceded that the IPRs were "not concluded" because it planned to seek rehearing. Appx13132. The district court denied Janssen's motion, doubting that § 315(e)(2) compelled the "absurd and unintended result" of applying estoppel against the *victor* in an IPR and desiring to create a complete record on invalidity. Appx20941-20944.

The district court then held a nine-day bench trial, evaluated extensive post-trial briefing, and issued its merits decision. Applying the *Phillips* standard, the court construed the claims more narrowly than the PTAB, limiting "treating" to anti-cancer effects. Appx4081. The court found that Appellees' proposed labels would indirectly infringe under that construction (without addressing underlying direct infringement), Appx123-142, and that the claims had adequate written-description support, Appx100-102, but that the claims were invalid for obviousness over prior art that included O'Donnell, Barrie, Gerber, and Sartor, Appx102-123.

The district court found that O'Donnell and Barrie had identified abiraterone as a treatment for prostate cancer before the '438 patent's priority date. Appx114. Citing Gerber, the court found that the combination of ketoconazole and prednisone was known to be safe and effective at treating refractory prostate cancer. Appx110, Appx116. Both Barrie and O'Donnell had described abiraterone as an even more selective CYP17 inhibitor than ketoconazole, Appx114, and the court found that a POSA "would have interpreted ketoconazole's clinical use as a basis to take the next investigative steps with abiraterone," Appx116. That included co-administration of prednisone because prior art suggested that co-administering a supplementary glucocorticoid would address abiraterone's adverse effects on adrenal function. Appx117. The district court further found that POSAs considered glucocorticoids to be reasonably tolerable, Appx118, and understood that prednisone could decrease PSA levels in prostate-cancer patients, Appx109. In view of the prior art, the claimed combination looked "less like serendipity and more like inevitability." Appx106.

The district court also considered Janssen's arguments regarding secondary considerations including commercial success, skepticism, long-felt need, and industry praise, but found the evidence unpersuasive. Appx118-123. Weighing all four *Graham* factors, the court found clear and convincing evidence that the claims were obvious. Appx123.

Along the way, the court again rejected Janssen's assertion that Appellees' tentative victory in the IPRs estopped Appellees from arguing obviousness in the litigation. Appx98-99. It disagreed that "Congress intended to require a party to stand mute in court because it previously prevailed on the same issue before the PTAB." Appx98. It also noted that Janssen's rehearing requests remained pending before the PTAB and alternatively concluded that the PTAB's decisions were not final, as required to trigger estoppel. Appx99.

C. The district court, this Court, and the Supreme Court all rejected Janssen's requests for an injunction pending appeal

Because several Appellees had tentative FDA approval to launch generic alternatives to Zytiga, Janssen moved to enjoin their launches pending appeal. Janssen's theory was that despite the four obviousness determinations, it was automatically entitled to delay Appellees' FDA approval under 35 U.S.C. § 271(e)(4)(A) because Appellees were statutorily estopped from asserting obviousness and had not prevailed on their other defenses. The district court denied that motion but issued a temporary stay/injunction to allow Janssen to seek emergency relief from this Court. Appx20635-20640; Appx150-151. This Court likewise denied an injunction but expedited the appeal. Dkts. 68, 72. Janssen then sought emergency relief from the Supreme Court, but it too refused. No. 18A539 (U.S. Nov. 30, 2018) (Roberts, Circuit J., in chambers). Several Appellees launched, and a robust generic market formed.

D. The PTAB denied Janssen's rehearing requests

In December 2018, the PTAB denied Janssen's long-pending requests for rehearing in the IPRs. In each case, the Board concluded that Janssen merely reargued previously rejected factual issues. Appx226-234; Appx298-305; Appx378-384.

This Court consolidated the ensuing appeals with Janssen's district-court appeal. Dkt. 86.

SUMMARY OF ARGUMENT

I. This Court should affirm the PTAB's obviousness determinations.

Janssen's PTAB appeals turn on its contention that "treating" prostate cancer with abiraterone and prednisone requires the prednisone to have an independent anti-cancer effect. But Janssen waived that argument. In the first (*Amerigen*) IPR, the Board adopted the patentees' definition of "treating," which "include[d]" but was not limited to anti-cancer effects. The Board emphasized that its construction did not require prednisone to have its own anti-cancer effect when it denied rehearing of its institution decision, and Janssen adopted the Board's construction.

Furthermore, the Board properly concluded that the broadest reasonable construction of "treating" prostate cancer includes therapeutic benefits such as reducing patient discomfort and offsetting abiraterone's side effects. Nothing in the claim language requires an anti-cancer-effect-only construction. The specification confirms that "treating" is not limited to anti-cancer effects by repeatedly stating that

the co-administered agent may be *either* "an anti-cancer agent" *or* "a steroid" and noting that prednisone is a steroid. The prosecution history accords: the examiner rejected the claims over a reference that described prednisone as palliating pain and relieving toxicity of other drugs, not as independently fighting cancer, and Janssen never disputed that.

Janssen's merits arguments depend on and fall with its claim construction. In any event, the disputes were factual, and substantial evidence supported the PTAB's findings under either construction. Janssen argues there was no reasonable expectation of success in developing a therapy in which prednisone had independent anti-cancer effect. But as the PTAB found, Sartor taught that prednisone reduced PSA levels, suggesting that it combatted cancer. That effect was not yet certain, but the law does not require certainty, only a *reasonable expectation* of success.

The Board was also entitled to find that Janssen's objective evidence of non-obviousness was weak. The Board reasonably found there was no long-felt need because other treatments were available. It reasonably found that the commercial success of Janssen's abiraterone-only product was largely due to the abiraterone itself (a prior-art product) and Janssen's blocking patent on abiraterone, not the claimed combination therapy. And it was similarly entitled to find no nexus between the claimed invention and the skepticism and failure of others alleged by Janssen.

II. If this Court affirms in any of the PTAB appeals, it need not reach the district-court appeal. Nevertheless, the district court did not clearly err in finding the claims obvious, and it correctly concluded that § 315(e)(2) did not estop Appellees from arguing obviousness at trial.

The district court did not err, much less clearly err, in assessing obviousness. Rather than assuming a motivation to pursue abiraterone, it detailed numerous prior-art references that pointed to abiraterone as a promising prostate-cancer treatment. Janssen's counterarguments raise factual issues that the district court reasonably resolved. The district court also found a reasonable expectation of success in achieving the claimed invention. Based on extensive evidence, the court found that both abiraterone and prednisone were considered promising prostate-cancer treatments and that POSAs had good reasons to administer them together.

The district court also properly analyzed secondary considerations. It balanced all the evidence together, found that Appellees carried their burden of proof, and made no clearly erroneous fact-findings. Like the PTAB, it properly found that Janssen's blocking patent and Zytiga's lack of prednisone undercut Janssen's commercial-success argument. It also properly found no strong evidence of skepticism, long-felt need, or unexpected results. Those were factual issues, and Janssen cannot retry them here.

Janssen's estoppel argument hinges on the false premise that § 315(e)(2) is a choice-of-forum provision. It is instead a collateral-estoppel provision, and it did not apply here for two reasons. First, § 315(e)(2) estoppel does not bar *prevailing* PTAB petitioners from maintaining invalidity defenses in district court. The statute should be construed consistent with traditional collateral-estoppel principles. Collateral estoppel is a consequence of losing, and Appellees did not lose. Estoppel is designed to promote consistency, and Janssen's construction produces inconsistency. No legislative history suggests that Congress intended to turn those traditional principles on their head and produce absurd results such as automatic injunctions against generic launch despite PTAB unpatentability findings. Second, the PTAB's January 2018 rulings were on rehearing and thus not final when the district court ruled. Section 315(e)(2) requires a "final written decision under section 318(a)," and §§ 318(a) and 319 equate finality with appealability. Janssen's argument that any paper labeled "final written decision" produces estoppel elevates form over substance.

III. If this Court does not affirm in any of the four appeals, it should remand to the PTAB and the district court. Janssen demands reversal of the district-court judgment and an order revoking Appellees' FDA approvals, but that would be improper. Any errors in weighing the evidence would at most warrant a remand, and statutory estoppel would not apply because vacaturs would nullify the Board's final

written decisions. Furthermore, the district court made two errors in its infringement analysis: Janssen did not prove indirect infringement under the district court's construction because FDA never approved using prednisone for anti-cancer effects, and the court never found direct infringement, a prerequisite to indirect infringement. At minimum, this Court would need to remand for the district court to decide whether to stay the case pending final resolution of the IPRs.

ARGUMENT

I. This Court should affirm the PTAB's obviousness determination

Janssen's arguments in the IPR appeals all turn on the PTAB's supposed error in not construing "a therapeutically effective amount of prednisone" to require the prednisone to have an anti-cancer effect. More specifically, Janssen contends that the claimed "therapeutically effective amount" of prednisone must "treat" prostate cancer and that the Board erred in construing "treating" prostate cancer to include palliative effects and reducing side effects of co-administered abiraterone.

As a threshold matter, Janssen waived that argument, most clearly in the first (*Amerigen*) IPR, by not contesting the Board's construction. This Court can thus affirm the *Amerigen* judgment without reaching any other issues, which would moot the other two IPR appeals because *Amerigen* addressed all 20 claims. Even if the

issue were preserved, the Board properly adopted the broadest reasonable construction, and substantial evidence supported the Board's obviousness determinations under either construction.

A. Janssen waived its objection to the Board's construction of "treating" prostate cancer

This Court should not reach Janssen's claim construction argument because Janssen failed to preserve it, most clearly in the *Amerigen* IPR.

As a general rule, "appellate courts do not consider a party's new theories, lodged first on appeal." *Sage Prods., Inc. v. Devon Indus., Inc.*, 126 F.3d 1420, 1426 (Fed. Cir. 1997). Janssen never proposed a construction that "treating" prostate cancer is limited to anti-cancer effects or excludes palliation and reducing abiraterone's side effects. It cannot do so for the first time here. *See VirnetX Inc. v. Apple Inc.*, 665 F. App'x 880, 883-84 (Fed. Cir. 2016) (construction arguments not presented to Board were waived); *Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 582 F.3d 1288, 1296 (Fed. Cir. 2009) ("If a party fails to raise an argument before the trial court, or presents only a skeletal or undeveloped argument to the trial court, we may deem that argument waived on appeal."); *MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284, 1294 n.3 (Fed. Cir. 2015) (finding waiver in IPR appeal where argument was raised in "a few scattered sentences at the oral hearing").

Amerigen's petition explained that the '438 patent defines "treatment" as "including 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.'" Appx29298 (quoting Appx759 ('438(3:46-50))). Janssen's preliminary response accepted Amerigen's definition of "treating" and defined "therapeutically effective amount of prednisone" as "an amount of prednisone effective for treating cancer." Appx29394-29395.

The PTAB's institution decision adopted the specification's definition of "treating," Appx156, accepted Janssen's construction of "therapeutically effective amount of prednisone," Appx157-158, and found, based on Amerigen's expert's opinion, that "'one of skill in the art would have expected that the co-administration of prednisone with abiraterone would improve the safety and tolerability of administering abiraterone by *reducing the potential for side effects* associated with the administration of a CYP17 inhibitor.'" Appx164-165 (emphasis added) (quoting Appx29316). The Board thus expressly concluded that "reducing the potential for side effects" was within the scope of prostate-cancer "treatment."

Janssen requested reconsideration of the institution decision, arguing that Amerigen's expert "ignore[d] the portion of the Board's claim construction that requires that the prednisone have a therapeutic anti-cancer effect for treating prostate cancer." Appx29460. But the Board denied rehearing, observing that "[a]lthough Patent Owner does not advocate for a new construction in its Request for Rehearing, its arguments are based on a construction that we have not adopted, namely that

'treating' must mean 'having an anti-cancer effect on.'" Appx174 (citing Appx29458-29460). Janssen was thus on notice that the Board's construction did *not* require prednisone to have an anti-cancer effect. If Janssen disagreed, it needed to say so in its upcoming patent-owner response. 37 C.F.R. § 42.71(d) (rehearing requests may not raise new arguments); Appx29443 (Scheduling Order) ("The patent owner is cautioned that any arguments for patentability not raised ... in the response will be deemed waived."); Appx14655 (Office Patent Trial Practice Guide).

Janssen did advance an anti-cancer-effect-only construction in *district-court* briefing three months before filing its patent-owner response in the *Amerigen* IPR. Appx3507-3521. The district-court brief quoted the same specification lexicography on which the Board relied but proposed excising the word "include" on grounds that although that term "in some instances may allow for other unnamed effects," "that is plainly not the case here." Appx3516-3518. But Janssen made no such argument in its patent-owner response in the IPR, where the broadest-reasonable-construction standard applied. Instead, Janssen endorsed *the Board's* construction:

> The [Institution Decision] further *properly* construes the terms "treat," "treating" and "treatment" to "*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."

Appx29550 (quoting Appx156) (emphases added).

Janssen also did not challenge the Board's construction or advocate for a narrower, anti-cancer-effect-only construction at the oral hearing. To the contrary, Janssen argued that "prednisone enhanced the anticancer activity of the abiraterone," Appx30072, and disputed whether a POSA would have turned to prednisone to treat abiraterone's side effects, Appx30072-30085. *See also* Appx30093-30094. Janssen never suggested that ameliorating abiraterone's side effects was insufficient to practice the claims even though, in Janssen's words, "this [wa]s not a case where [Amerigen was] arguing that the prednisone is there for an anticancer effect." Appx30085.

In short, rather than raising a claim-construction dispute, Janssen adopted the Board's construction of "treating" as including more than anti-cancer effects and made factual arguments that the references did not teach that prednisone would reduce abiraterone's side effects. The Board's January 2018 decision accordingly maintained the constructions from its institution decision, Appx182-185, and focused on the disputed factual issues, Appx189-220.[2] Raising the issue in a rehearing

[2] The Board's January 2018 decision mentioned the district court's omission of the word "includes" when interpreting "treating" as limited to anti-cancer effects. Appx184-185. But the Board did so on its own, consistent with *Power Integrations, Inc. v. Lee*, 797 F.3d 1318, 1326-27 (Fed. Cir. 2015), not because Janssen argued for the district-court construction. The Board also discussed its construction and the basis in the specification when analyzing the reasonable expectation of success. Appx204-208. Again, however, the Board did so on its own, not because Janssen contested that construction.

request would have been too late, 37 C.F.R. § 42.71(d), and Janssen's rehearing request accordingly focused on factual issues without contending that the Board erred in its claim construction. Appx30135-30151.

Because Janssen's arguments in the IPR appeals all depend on its claim-construction theory and Janssen failed to preserve that argument in the *Amerigen* IPR, this Court can and should affirm in that appeal on waiver/forfeiture grounds alone. And because affirmance in any of the IPRs resolves the whole case, this Court can and should dispose of the whole case on that basis.

B. The Board properly adopted the broadest reasonable construction of "treating" prostate cancer

Even if Janssen preserved its claim-construction argument, the PTAB properly concluded that using prednisone to "treat" prostate cancer in a human includes not only using it for anti-cancer effects, but also using it for other therapeutic benefits such as reducing patient discomfort and offsetting side effects of CYP17 inhibitors. Under then-governing regulations, the Board had to apply the broadest reasonable construction of the claims. 37 C.F.R. § 42.100(b) (2017); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144-46 (2016). The Board's construction was reasonable.

Claim 1 recites "[a] method for the treatment of a prostate cancer in a human" that comprises administering "a therapeutically effective amount of prednisone" along with abiraterone. Appx765 ('438(16:16-20)). Nothing in that language limits

prednisone "treatment" to anti-cancer effects or excludes palliation or countering abiraterone's side effects.

Nothing in the specification imposes such a requirement, either. The specification defines a "therapeutically effective amount" of a "therapeutic agent" as an amount "effective for treating a disease or disorder ... such as cancer." Appx759 ('438(4:17-22)). In the same section, it defines "treating" to

> *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.

Id. ('438(3:46-50) (emphasis added)). Notably, the specification defined "treating" open-endedly ("includ[ing]" certain effects) but gave other terms closed-ended definitions. Appx759-760 ('438(3:29-5:5)). Moreover, the partial definition of "treating" broadly refers to "management" and "control" of cancer, which are not limited to attacking cancer cells. The PTAB properly adopted the patentees' lexicography, Appx184-185; *see Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1380 (Fed. Cir. 2009), and nothing in those definitions limits "treating" cancer to anti-cancer effects.

The remainder of the specification confirms that "treating" and "therapeutic effects" are not limited to anti-cancer effects. The patent makes clear that the "therapeutic agent" combined with the CYP17 inhibitor may be *either* "an anti-cancer agent" *or* "a steroid." Indeed, the specification *repeatedly* describes the invention

as methods for "treating" cancer comprising a CYP17 inhibitor such as abiraterone in combination with an "additional therapeutic agent such as an anti-cancer agent *or a steroid*." Appx755-758 ('438(Abstract, 1:5-16)) (emphasis added); *see also* Appx758-760 ('438(2:9-16, 3:12-20, 5:9-17, 10:53-56)) (nearly identical language). If the patentees meant to limit "treating" and "therapeutic agents" to anti-cancer agents, they would not have separately highlighted steroids, which had long been used to ease the suffering of cancer patients and were known to offset adverse side effects of CYP17 inhibitors such as reduced adrenal cortisol production. And as the Board reasoned, Appx358, there would have been no reason to address steroids separately if steroids could not "treat" cancer by providing therapeutic benefits other than anti-cancer effects.

The specification expressly identifies prednisone as a glucocorticoid, and it identifies glucocorticoids as steroids. Appx758-765 ('438(1:14-16, 5:9-17, 9:40-44, 10:14-20, 10:25-41, 15:66-16:2)). It also lists prednisone among many agents that can serve as antibiotics and thus as "anti-cancer agents," Appx759, Appx762 ('438(3:16-20, 9:30-44)), but it repeatedly describes using prednisone as a steroid with no mention of anti-cancer effects, Appx762-765 ('438(10:15-21, 10:25-41, 13:6-10, 13:18-21, 15:66-16:3)). The specification thus supports the Board's conclusion that prednisone may "treat" cancer by producing familiar steroid effects (palliation and reducing side effects) *or* by having anti-cancer effects of its own.

The prosecution history supports this reading. The examiner repeatedly rejected the claims over the combination of O'Donnell, which discussed abiraterone's anti-cancer effects, and Tannock, which discussed co-administering prednisone with other anti-cancer drugs to treat refractory prostate cancer. Appx25938-25942; Appx25983-25989; Appx26023-26029. Tannock did not describe prednisone as providing independent anti-cancer effects; it characterized "the goal of treatment" as palliation and described prednisone as providing palliation and relief from toxicity of anti-cancer drugs. Appx23063-23073. Janssen did not distinguish Tannock on grounds that Tannock did not describe prednisone as having anti-cancer effects. Appx25980-25981; Appx26006-26007; Appx26047-26049. Janssen certainly did not disclaim a broader reading of "treating." The Board's construction of "treating" was therefore reasonable.

Janssen's contrary arguments are unavailing. Janssen first argues that what is being treated is the cancer, not the patient. But the claims refer to "treatment of a prostate cancer *in a human*," Appx765 (16:16-17) (emphasis added), and if an anti-cancer drug like abiraterone produces intolerable pain or suppresses production of beneficial compounds, it is perfectly sensible to describe a co-administered steroid such as prednisone that improves the patient's tolerance and well-being as a part of a cancer "treatment" that has "therapeutic effects." Clinicians routinely describe

"treating" the flu with anti-inflammatories and fluids, whether or not anti-viral medications are also used. And nothing in the intrinsic evidence compels Janssen's artificial distinction between treating cancer and treating a cancer patient.

Janssen suggests that under the Board's construction, one could practice the invention without providing any anti-cancer effect. But the claims recite administering a *combination* of prednisone and abiraterone, and abiraterone was known for its anti-cancer effect. The claimed methods treat prostate cancer because they require administering abiraterone, and abiraterone is better tolerated when taken with prednisone. Janssen notes that several dependent claims recite cancer "not responding to at least one anti-cancer agent," but that relates to the "refractory prostate cancer" limitation, not to the meaning of "treating" or "therapeutic effect."

Janssen also points to the specification's statement that a steroid should be administered in "an amount that is sufficient to treat the cancer." Appx762 ('438(10:21-24)). But that begs the question of what "treating" cancer means. Moreover, Janssen omits the remainder of the passage, which says "whether administered alone or *in combination* with [abiraterone]." *Id.* (emphasis added). Janssen did not claim a method of treating prostate cancer by administering prednisone alone; it claimed a method of treatment using prednisone in combination with abiraterone. In any event, the specification makes clear that a "therapeutic agent" can be *either* an "anti-cancer agent" *or* a steroid (or in prednisone's case, both).

Janssen next argues that the Board's reading of "include" renders the specification's definition of "treatment" meaningless. Janssen is mistaken. The specification teaches that "treating" *includes* causing certain effects, but that does not mean it has no boundaries. The Board did not extend "treatment" to cover "any effect on the body," as Janssen suggests—only to effects of prednisone related to prostate-cancer treatment as described in the prior art. The palliative and cortisol-replacement effects of prednisone are closely related to the overall aims, utility, and effectiveness of the claimed method. *See* Appx38596-38597.

Finally, Janssen contends that "include" should be read restrictively, as requiring one or more of the listed effects. But even if that is *a* reasonable construction, it is not the *broadest reasonable* construction. None of Janssen's cases hold that "including" always means that the named elements are essential. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003), announced no such rule. The Court addressed the term "comprising" when used as a term-of-art "in claim language": e.g., widgets "comprising" A and B must include A and B and may include other components. The Court also noted that "including" may be a synonym for "comprising." *Id.* at 1344-45. But the holding relied on the use of "comprising" as the transition in the claims. *Id.* at 1345 ("[R]ead properly in light of the term 'comprising,' this means that the claimed glycoprotein must have—at minimum—all 166 amino acids shown in Figure 6."). The other decisions Janssen

cites likewise concerned uses of "including" as a transition phrase in claims, not as ordinary descriptive language in a specification. *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, the Board reasonably interpreted the statement that "treating" "include[s]" A and B as not precluding C, just as a statement that pets "include" cats and dogs would not exclude pet rabbits. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1302 (Fed. Cir. 2006) (specification's use of "included" was "non-limiting" and "suggest[ed] some persons, but not all persons, who may benefit from the invention").

C. Substantial evidence supported the Board's determination that the claims were obvious under either claim construction

Janssen argues that the PTAB's construction "infected" the PTAB's obviousness analysis. It did not. The Board found that the claims were obvious under either reading of "treating" prostate cancer with prednisone, and substantial evidence supported those findings.

1. The Board identified extensive evidence of a reasonable expectation of success

Janssen does not challenge the PTAB's findings that POSAs were motivated to pursue abiraterone and administer it with prednisone. Janssen instead argues that the Board failed to find that POSAs reasonably expected success in developing a combination therapy in which both drugs have anti-cancer effects. That argument

fails if this Court rejects Janssen's premise that prednisone must have an independent anti-cancer effect. *See* Appx203-208; Appx272-276. It also fails even if the Court accepts Janssen's claim-construction premise.

"[T]he expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). In the *Wockhardt* IPR, the PTAB found that Sartor taught that prednisone independently reduced levels of PSA (indicating anti-prostate-cancer activity) and thus appeared to have an anti-cancer effect in some patients. Appx337, Appx349-353. Prednisone alone was "tolerated and effective" for prostate cancer and showed "some measure of efficacy" against refractory prostate cancer. Appx350-351 (citing Appx45665, Appx45668-45669). The Board specifically found that Wockhardt established a reasonable expectation "that prednisone would 'treat' prostate cancer" even under a narrower definition of "treat." Appx359.

Janssen complains that the Board did not find that prednisone and abiraterone would fight cancer when used together. But the Barrie patent, O'Donnell, and others taught that abiraterone fought cancer, and Sartor taught that prednisone likely did. The claims require no special synergy, and the Board did not find that abiraterone and prednisone were incompatible. Janssen accuses the Board of misapplying the burden of proof, but the Board expressly recognized the petitioner's "burden [to

show] that the prior art provide[d] a reasonable expectation that prednisone could be used as a therapeutic agent in the treatment of prostate cancer." Appx359.

Janssen points to a statement in a 2006 Sartor article that glucocorticoids such as prednisone had not "demonstrated a survival advantage." But the claims do not require a survival advantage, and a reasonable expectation of success does not require established proof of efficacy. Furthermore, Sartor 2006 did not say that glucocorticoids had no anti-cancer effect, only that "because no study with [secondary hormonal manipulations] has *demonstrated* a survival advantage, *their potential role is not agreed upon by all*." Appx44462 (emphasis added). If anything, that equivocal statement suggested that more research was needed to prove efficacy. The Board was not compelled to infer no reasonable expectation of success.

Janssen similarly argues that PSA responses to glucocorticoids were modest and short-lived, but that was just Janssen's expert's view. The Board was not required to credit it, and in any event the claims contain no duration or degree requirements. Nor can Janssen fall back on Appellees' experts' testimony. Prednisone's effect in combination with abiraterone may not have been certain, but the law requires only a *reasonable expectation* of success. There was substantial evidence that prednisone was believed to have anti-cancer effects, *see* Appx41340-41341 (citing, *e.g.*, Appx45665-45667; Appx45579-45581; Appx46526), and the Board was entitled to credit that evidence.

2. The Board reasonably concluded that Janssen's objective evidence of non-obviousness was weak

The Board was also entitled to find that Janssen's evidence of secondary considerations was unpersuasive. At bottom, these were factual issues, and substantial evidence supported the Board's findings under both constructions of "treat."

Long-felt, unsolved need. Janssen argued that no pre-existing treatment "could extend the life of mCRPC patients" and that there was an urgent need for treatments "that would improve survival." Appx41698. But the '438 claims require neither improved survival nor treating mCRPC patients. They require an effective treatment for a prostate cancer, and the Board reasonably found that other treatments were available and that there was no long-felt, unsolved need for the claimed regimen in particular. Appx366 (citing Appx45572; Appx42589).

Commercial success. Janssen contends that the Board should have presumed a nexus between commercial success of Zytiga (abiraterone alone) and the claimed combination treatment and that the Board erred by requiring Janssen to prove the nexus. But Janssen bore the burden of proving that Zytiga's commercial success was due to the claimed combination treatment. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010). A nexus may be presumed when the successful product and the claimed invention are the same, but that was not the case here: Zytiga does not contain prednisone. Moreover, the PTAB found that Appellees rebutted any presumption. In particular, it found that Zytiga's commercial success was not strong

evidence of non-obviousness because (a) Janssen had a blocking patent on abiraterone that deterred others from exploring the commercial potential of abiraterone-based therapies, Appx217-218; Appx287-288; Appx368-369; and (b) it was unclear whether Janssen's sales of abiraterone were due to the claimed combination treatment method or the known, previously-patented abiraterone component, Appx218-219; Appx289-290; Appx369-370. Those findings were well-supported and consistent with law.

"Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). But that theory breaks down when a blocking patent impedes others from pursuing the claimed invention. *Id.* at 1376-77; *see also Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740-41 (Fed. Cir. 2013) (inference of non-obviousness from commercial success was weak where patents blocked entry until long after claimed invention). In *Acorda Therapeutics, Inc. v. Roxane Laboratories, Inc.*, 903 F.3d 1310 (Fed. Cir. 2018), this Court recognized that whether blocking patents deter innovation in the blocked space depends on case-specific facts. *Id.* at 1337-39. Citing expert testimony, the Court affirmed that a blocking patent deterred non-licensees from developing the invention and held that

the trial court properly discounted the plaintiff's evidence of commercial success. *Id.* at 1337-41.

The facts here supported the same result. Expert testimony showed that the Barrie patent, which claimed abiraterone and methods of using it to treat prostate cancer, blocked everyone but Cougar from pursuing an abiraterone-prednisone combination treatment from 2004 until that patent expired in 2016. Appx30440-30445; Appx38886-38890; Appx46888-46893. Even if Janssen had actively shopped the Barrie patent before 2004, which was disputed, the patent was a deterrent, and it was locked up before O'Donnell published the first human studies of abiraterone.[3]

The PTAB was also entitled to find no nexus because it was unclear that the commercial success of Janssen's abiraterone product was due to the claimed combination treatment rather than abiraterone itself. Janssen's prescribing literature and expert testimony indicated that most, if not all, of the anti-cancer effects came from the abiraterone and that prednisone was co-administered to reduce adverse reactions. Appx218-219 (citing Appx30486-30489; Appx30202-30208; Appx30507-30508); Appx289-290 (citing Appx38909-38912; Appx38930-38931; Appx38614-38618);

[3] Janssen notes that original licensee Boehringer halted its development program, but Janssen presented no evidence of *why* it did so, which could have been for many reasons. *See* Appx42449-42450; Appx42683.

Appx369-370 (citing Appx46691-46694; Appx46785-46786). This was a fact dispute, and substantial evidence supported the Board's finding.

Skepticism and failure of others. Janssen asserted that difficulties in finding research sponsors suggested "skepticism about the effectiveness of abiraterone acetate monotherapy" and showed that "abiraterone acetate had been relegated to the back-burner." Appx41696-41697. Janssen also highlighted alleged failures in developing other agents "for treating advanced prostate cancer." Appx41697. But the totality of evidence showed that many researchers (e.g., O'Donnell) were enthusiastic about abiraterone, especially in combination with a glucocorticoid. The Board considered Janssen's evidence and reasonably found it unpersuasive because the claims require administering abiraterone with prednisone, yet Janssen's evidence addressed "purported skepticism of the industry toward abiraterone acetate alone." Appx365. Janssen's evidence of failure of others was likewise divorced from the claims, which do not require treating "advanced prostate cancer" or mCRPC. The Board also reasonably credited evidence that the Barrie patent, which claimed abiraterone itself, had discouraged development of abiraterone-based therapies. Appx365; Appx369.

In short, the secondary considerations turned on factual issues, and substantial evidence supported the PTAB's findings. The Board reasonably concluded that

Janssen's evidence did not outweigh the strong prior-art evidence that the claims were obvious. Appx219-220; Appx290-291; Appx370-371.

D. This Court need not reach the district-court appeal if it affirms any of the PTAB's unpatentability determinations

If the Court affirms any of the PTAB's unpatentability determinations, it should dismiss Janssen's appeal from the district-court judgment. Each IPR covered every claim of the '438 patent, and Janssen cannot pursue damages or an injunction on claims whose unpatentability has been affirmed. *XY, LLC v. Trans Ova Genetics, L.C.*, 890 F.3d 1282, 1294 (Fed. Cir. 2018) (affirmance in PTAB appeal required dismissal of co-pending district-court appeal because affirmance "ha[d] an immediate issue-preclusive effect on any pending or co-pending actions involving the patent"). That is so even though the PTAB and district-court analyses were not identical. *MaxLinear, Inc. v. CF CRESPE LLC*, 880 F.3d 1373, 1376-77 (Fed. Cir. 2018). Section 315(e)(2) is irrelevant because the result would stem from this Court's judgment in an IPR appeal, not from any invalidity argument in the district court.

II. This Court should affirm the district court's obviousness determination if it does not dismiss Janssen's appeal

If this Court reaches the district-court appeal, it should affirm the district court's obviousness determination and affirm that Appellees' not-yet-final victories in the PTAB did not estop Appellees from maintaining their obviousness defenses in the district court.

A. The district court correctly found that the claimed combination of abiraterone and prednisone was obvious over the prior art

Janssen's challenges to the district court's obviousness determination are really challenges to factual findings, and none of those findings was clearly erroneous.

1. The district court properly found a motivation to pursue abiraterone as a prostate-cancer treatment

Janssen first accuses the district court of assuming, rather than finding, that POSAs had a reason to pursue abiraterone as a prostate-cancer therapy in 2006. But the court detailed numerous references that pointed to abiraterone as a promising prostate-cancer treatment. Appx106-108, Appx114-115. As the court observed, "multiple experts had concluded that it was worth pursuing abiraterone as a treatment for prostate cancer." Appx121.

Abiraterone was known to be a selective CYP17 inhibitor that was superior to ketoconazole in blocking androgen production. Barrie's 1994 article, Appx23056-23062, observed that abiraterone was more potent and selective than ketoconazole and thus "worthy of further study" as a potential agent "for the treatment of hormone-dependent prostate cancer." Appx106-107 (citing Appx23060; Appx22479). Potter's 1996 article, Appx27726-27736, also recognized this, Appx107 (citing Appx27731-27732; Appx22232; Appx22479), and Jarman's 1998 article, Appx23078-23086, noted that abiraterone had been selected for testing of its androgen-inhibiting capability in animals. Appx107 (citing Appx23080). Human trials

of abiraterone began in the late 1990s, and the results, reported in O'Donnell's 2004 article, Appx23171-23179, showed that it was a promising second-line treatment. Appx107-108 (citing Appx23171-23172; Appx23213-23214).[4]

If anything, abiraterone was gaining momentum in 2006. Vidal's 2004 article reported that abiraterone inhibited adrenal androgen synthesis. Appx23182-23183. Attard's 2005 review recounted O'Donnell's results, concluded that CYP17 inhibitors were "a logical target for the development of new drugs to treat CRPC," and observed that abiraterone was the "most potent and selective" of them. Appx27910-27915. Garnick's 2006 book chapter, Appx23209-23222, hailed abiraterone as "show[ing] potential in the treatment of cancer" with an "ability to selectively inhibit the target enzyme" and thus "inhibit[ ] ... testosterone production in both the adrenals and the testes." Appx23213-23214 (cited at Appx108). Garnick also reported that abiraterone was "under development as a second-line hormonal therapy for prostate cancer." Appx23214. And the '438 patent itself confirmed that abiraterone and

[4] Janssen suggests that delays in O'Donnell's publication show skepticism of those results, but the district court properly rejected that inference as unsupported speculation. Appx114 n.118. One reviewer complained that the early draft was unclear, while another found the results interesting and abiraterone promising, and ultimately a revised, clarified version was published in the distinguished *British Journal of Cancer*. Appx21138-21139; Appx21151-21154; Appx22901-22903; Appx27876-27879; Appx21143.

other CYP17 inhibitors had previously "been shown to be useful in the treatment of ... disorders like prostate cancer." Appx760 ('438(5:23-29)).

The district court thus found that abiraterone "had been identified in the prior art as a second-line prostate cancer treatment" that was superior to ketoconazole because it selectively inhibits CYP17, which is key to androgen production. Appx114-115. That provided ample motivation to continue investigating abiraterone.

Janssen's counterarguments at most raised fact disputes for the district court to resolve. According to Janssen, the court found a "prevailing belief" that prostate cancer became androgen-independent after it resumed growing following androgen-deprivation therapy. But in the same paragraph the court observed a "significant divergence" of opinion on that score. Appx87. As discussed above, many researchers had found abiraterone to be a promising second-line treatment, all the way through 2006. Some writers still used the terminology "androgen-independent" and "hormone-resistant," but that did not indicate rejection of abiraterone, much less all second-line treatments. Indeed, O'Donnell referred to "androgen-independent prostate cancer" and nevertheless promoted abiraterone's potential as a second-line treatment. Appx23171, Appx23178. The 2005 national prostate cancer treatment guidelines likewise urged continued testosterone suppression in "patients with 'hormone refractory prostate cancer.'" Appx25810; Appx25846-25847.

Other researchers were pursuing other approaches, some "perhaps even more promising." Appx117. But that is normal in large fields studying widespread diseases—witness the many treatments for hypertension. The question was not whether abiraterone was the single most promising avenue for treating prostate cancer, just whether there was a motivation to pursue it among others. *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012); *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). The district court properly found there was.

2. The district court properly found a reasonable expectation of success in combining abiraterone and prednisone

The district court found multiple motivations to supplement abiraterone with prednisone in prostate-cancer treatment regimens: prednisone was thought to reduce side effects of CYP17 inhibitors such as reduced cortisol, to improve patient comfort (palliate), and to have anti-tumor effects of its own, and there was a broader trend toward combination therapies. Appx108-112, Appx114-117.

Janssen does not challenge the district court's finding of a motivation to combine. It instead argues that POSAs had no reasonable expectation of success because neither abiraterone nor prednisone was thought to combat cancer. But again, the law requires only a *reasonable expectation* of success, not certainty. *In re Copaxone Consol. Cases*, 906 F.3d 1013, 1026 (Fed. Cir. 2018). Whether there was such a reasonable expectation was disputed, and the district court found there was.

Appx118 ("[T]o the POSA, the prior art would suggest that abiraterone could be combined with prednisone with a reasonable probability of success.").

Appellees explained above why POSAs were motivated to pursue abiraterone as a second-line treatment for prostate cancer: it was known to be a potent and selective CYP17 inhibitor, and O'Donnell and others had shown it was effective in suppressing androgen production. Further study was warranted because O'Donnell did not directly measure longer-term anti-cancer effects, but there was a reasonable expectation of success based on over a decade of research.

Janssen argues that Boehringer had abandoned abiraterone, but as in the PTAB, there was no evidence of *why* Boehringer discontinued the project: Janssen's sole fact-witness was not involved and did not know. Appx21148-21149; Appx22985. A few other companies declined licenses, but Janssen's evidence was thin and the district court found that the licensing efforts had been "lackluster" and "desultory." Appx120; *see* Appx21149; Appx22985-22992. Moreover, Cougar licensed abiraterone in 2004, even before publication of O'Donnell.

Janssen's argument regarding prednisone also fails. To begin with, Janssen presumes that the district court correctly limited "treating" prostate cancer to anti-cancer effects. Janssen's argument fails if this Court concludes, as Appellees urged, Appx3590-3612; Appx3998-4012, that prednisone can "treat" prostate cancer by alleviating patients' suffering or abiraterone's side effects. Regardless, the district

court did not clearly err in finding a reasonable expectation that prednisone would fight cancer.

As the district court explained, Sartor's 1998 article taught that "prednisone can cause reduced PSA levels, a marker of anti-cancer effect," and thus recommended using prednisone to treat mCRPC patients. Appx115 (citing Appx23087-23091); *see also* Appx109. Sartor's conclusion that "prednisone can have an anti-cancer effect" was "supported by three other prior art references: Foss[å] 2001, Fakih 2002, and Harris 2002." Appx115 (citing Appx27786-27797; Appx23136-23144; Appx27829-27832). That provided a reasonable expectation of success even though the mechanism of action was not yet fully understood.

Janssen cites testimony from Appellees' infringement expert that he personally did not think that prednisone's anti-cancer benefit was "proven," but he was not opining as a POSA and "confirmed proof" is not the test. Janssen also cites conflicting evidence regarding prednisone's anti-cancer effects, but this Court is not a trial court. The district court heard the evidence and did not commit clear error in finding that POSAs reasonably expected prednisone to have an independent anti-cancer effect.

Finally, Janssen argues that it was uncertain whether the combination of abiraterone and prednisone would be effective. But again, certainty is not the standard. Drugs can have interaction problems, but many references had taught to use CYP17

inhibitors with corticosteroids, and no studies had proven that abiraterone and prednisone worked at cross-purposes.

3. The district court properly found that Janssen's evidence of secondary considerations was weak

Janssen raises procedural and substantive challenges to the district court's analysis of secondary/objective considerations. Both fall short.

The district court did not determine obviousness based on the prior art and then demand that Janssen prove that objective considerations required a different result. The court set forth the burden and standard of proof, Appx102, sequentially laid out the evidence on all four *Graham* factors, Appx103-113, and then stated its "overall conclusions as to obviousness" in view of the entire record, Appx106, Appx114-123. It gave objective considerations "less weight" because the evidence was "mixed at best," Appx113, and ultimately, "[b]alancing all of the prior art *and the other indicia*," concluded that Appellees established obviousness by clear and convincing evidence, Appx123 (emphasis added).

Janssen quarrels with the court's statement that objective considerations did not "alter" its conclusion, Appx118, but the Supreme Court said essentially the same thing in *KSR*: the patentee had "shown no secondary factors to *dislodge* the determination that [the claim-in-suit was] obvious." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 426 (2007) (emphasis added). Janssen also ignores *Intercontinental Great Brands LLC v. Kellogg North America Co.*, 869 F.3d 1336 (Fed. Cir. 2017), where

this Court rejected an argument that the district court dismissed objective considerations as an afterthought even though it addressed them after analyzing prior art and made the "not-uncommon choice of words" that they did not "overcome" the defendant's "extremely strong prima facie showing." *Id.* at 1345-46; *see also Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1353-54 (Fed. Cir. 2013) (similar).

On the merits, the district court committed no legal error and made no clearly erroneous fact-findings. The court recognized that Zytiga had "enjoyed commercial success" but, like the PTAB, found two partially offsetting factors: (1) Janssen had a blocking patent on abiraterone and methods of using abiraterone to treat prostate cancer, and (2) Janssen's sales of Zytiga (abiraterone alone) were not wholly attributable to the patented combination therapy. Appx118-120. That analysis was proper.

This Court has repeatedly recognized that the inference of non-obviousness from commercial success is weak where other patents blocked commercial entry. *Acorda*, 903 F.3d at 1337-41; *Galderma*, 737 F.3d at 740-41; *Merck*, 395 F.3d at 1376-77. Barrie's patent on abiraterone and methods of using it to treat prostate cancer blocked everyone but Cougar from pursuing an abiraterone-prednisone combination treatment from 2004 until 2016. Janssen argues that licenses were available

before 2004, but the district court found that Janssen's licensing efforts were "lack-luster" and "desultory," Appx120, and Cougar obtained exclusive rights before O'Donnell's encouraging report on the first human studies was published.

Janssen argues that the court should have presumed that Zytiga's commercial success was due to the claimed invention and then required Appellees to prove that the Barrie patent was an obstacle. But as discussed above, Janssen bore the burden of establishing that Zytiga's commercial success was due to the claimed combination rather than its abiraterone component. No presumption of nexus was warranted because the commercially successful product was abiraterone, and in any event Appellees showed that the blocking patent interfered with commercial competition. The court found, based on record evidence, that Zytiga's sales "may not be wholly attributable to the patented combination therapy" and that the blocking patent from 1997 to 2006 (and beyond) "discouraged entry at the very time when the obviousness of [the] combination therapy was manifesting itself." Appx119-120; *see* Appx21145-21146; Appx22950-22965. This Court should defer to those findings.

The district court also properly found no strong evidence of skepticism toward the claimed invention. Appx121. Some researchers were pessimistic about second-line therapies; others were not. As discussed above, many articles considered abiraterone promising. Moreover, the court correctly found that some of the skepticism was toward abiraterone alone, which was expected to have problematic side effects,

rather than a combination including a corticosteroid that ameliorated those side effects. Ultimately, the degree of skepticism toward the claimed invention was an issue reserved for the fact-finder.

The district court also did not clearly err in finding that Janssen's evidence of long-felt need and unexpected results was underwhelming. Appx121-122. Janssen cites FDA's priority-review approval of Zytiga, but FDA also prioritized other mCRPC drugs in the same timeframe, including Jevtana® and Xtandi®. Appx22542-22543. That simply shows that prostate cancer was an important problem that multiple companies were attacking in various ways. Janssen argues that the court should have been more impressed that Zytiga + prednisone improved survival time from 2½ to 4 months, but the court was entitled to consider that "a real improvement" and not a quantum leap. Janssen concludes by touting the combination's improved tolerability, but that ignores that reducing side effects was one of the motivations for adding prednisone to abiraterone.

At bottom, Janssen is improperly trying to retry its case in this Court. The strength of Janssen's objective-indicia evidence was a quintessentially factual issue, and the district court was entitled to find that evidence equivocal and overwhelmed by strong evidence that the claimed combination was "well-foreshadowed in peer-review articles." Appx123.

B. § 315(e)(2) did not estop Appellees from maintaining their obviousness defenses at trial and does not bar Appellees from defending the district court's judgment on appeal

Janssen alternatively argues that the district court should never have reached the merits. According to Janssen, § 315(e)(2) forced Appellees to choose between asserting unpatentability in the IPRs or in the district court, and once the PTAB issued a paper formally titled "Final Written Decision," Appellees could not pursue their invalidity defense in the district court. But § 315(e)(2) is not a choice-of-forum provision. It is an *estoppel* provision, and it did not apply here for two reasons. First, § 315(e)(2) estoppel, like other collateral estoppels, applies only to parties that have *lost*. It does not hamstring *prevailing* parties like Appellees, and it was not intended to produce inconsistent results. Second, the PTAB's decisions were not *final* when the district court invalidated the claims because Janssen had requested rehearing and the PTAB had not addressed those requests. The IPR decisions became final only *after* the district court's judgment was on appeal, and § 315(e)(2) does not preclude parties from defending previously entered invalidity judgments on appeal.

1. § 315(e)(2) is an estoppel provision, not a choice-of-forum provision

Section 315(e)(2) reads:

> (e) ESTOPPEL.—
>
> (2) CIVIL ACTIONS AND OTHER PROCEEDINGS.—The petitioner in an inter partes review of a claim in a patent under this chapter that results in a final written decision under

> section 318(a), or the real party in interest or privy of the petitioner, may not assert either in a civil action arising in whole or in part under section 1338 of title 28 or in a proceeding before the International Trade Commission under section 337 of the Tariff Act of 1930 that the claim is invalid on any ground that the petitioner raised or reasonably could have raised during that inter partes review.

By its terms, § 315(e)(2) is an "estoppel" provision that bars certain parties from litigating certain issues in certain other cases after a final written decision by the PTAB. Contrary to Janssen's suggestion, nothing in § 315(e)(2) requires an IPR petitioner to choose one forum and forgo another. The choice-of-forum provisions in § 315 are subsections 315(a)(1) and 315(b): § 315(a)(1) bars parties that have filed civil actions challenging validity from filing any IPR petitions on the same claims, and § 315(b) generally bars parties from petitioning for IPR more than a year after service of a complaint alleging infringement. *See also* 35 U.S.C. § 315(a)(2) (IPR petitioner may seek declaration of invalidity, but automatic stay may apply).

2. § 315(e)(2) does not limit assertions by prevailing petitioners

Sensibly read, § 315(e)(2) prevents an IPR petitioner that has *failed* to establish unpatentability from later pursuing invalidity defenses that it raised or could have raised in the IPR. It would be nonsensical, and raise serious due process concerns, to read § 315(e)(2) as stripping a defendant's 35 U.S.C. § 282(b)(2) right to raise an invalidity defense because it *succeeded* in proving unpatentability at the PTAB. *See King v. Burwell*, 135 S. Ct. 2480, 2489 (2015) ("[W]hen deciding

whether [statutory] language is plain, [courts] must read the words 'in their context with a view to their place in the overall statutory scheme.'").

The "'title of a statute and the heading of a section' are 'tools available for the resolution of a doubt' about the meaning of a statute." *Almendarez-Torres v. United States*, 523 U.S. 224, 234 (1998) (citations omitted). Section 315(e) is expressly an "estoppel" provision. "Estoppel" comes in various forms, but the form relevant here is *collateral* estoppel (issue preclusion) because § 315 describes the collateral consequence in a second case of a final resolution of an issue in a first case (the IPR). *See B&B Hardware, Inc. v. Hargis Indus., Inc*., 135 S. Ct. 1293, 1302-03 (2015).

Collateral estoppel is a consequence of *losing*: "'a losing litigant deserves no rematch after a defeat fairly suffered.'" *Id.* at 1303. Parties that have *prevailed* are not collaterally estopped. Furthermore, collateral estoppel is designed to promote consistency of results in different proceedings. "The idea is straightforward: Once a court has decided an issue, it is 'forever settled as between the parties,' thereby 'protect[ing]' against 'the expense and vexation attending multiple lawsuits, conserv[ing] judicial resources, and foster[ing] reliance on judicial action by minimizing the possibility of inconsistent verdicts.'" *Id.* at 1302-03. Limiting § 315(e)(2) estoppel to petitioners that have *lost* ensures consistency between PTAB and district-court results. Estopping petitioners that have *won* would produce *inconsistency*: an

IPR petitioner that has proven the invalidity of issued claims would be prevented from establishing invalidity in the district court and ITC on the same grounds.

Even the PTO acknowledges (at 4) that Janssen's construction is "counterintuitive." And settled statutory-construction principles counsel against it. "[W]here Congress borrows terms of art in which are accumulated the legal tradition and meaning of centuries of practice, it presumably knows and adopts the cluster of ideas that were attached to each borrowed word in the body of learning from which it was taken and the meaning its use will convey to the judicial mind unless otherwise instructed." *Morissette v. United States*, 342 U.S. 246, 263 (1952). Thus, "[w]here Congress uses terms that have accumulated settled meaning under … the common law, a court must infer, unless the statute otherwise dictates, that Congress means to incorporate the established meaning of these terms." *Neder v. United States*, 527 U.S. 1, 20-21 (1999) (citations omitted) (fraud offenses include materiality requirement because "fraud" had well-settled common-law meaning, even though under "'a natural reading of the full [statutory] text,' materiality would not be an element" (citation omitted)). Here, § 315(e)(2) "estoppel" should be construed like common-law collateral estoppel and read as preventing a losing petitioner from taking a second bite at the invalidity apple.

Nothing in § 315(e)(2) or its legislative history suggests that Congress intended to turn collateral estoppel on its head and tie the hands of an IPR victor in

litigation that happens to continue despite the PTAB's unpatentability ruling. In adopting the provision, Congress was concerned with preventing the "use [of] post-grant procedures for abusive serial challenges to patents," not with shielding patents already found unpatentable from further scrutiny. Appx14557 (statement of Sen. Grassley).

Janssen suggests that Congress intended to broaden the scope of the *inter partes* reexamination estoppel of pre-AIA § 315(c), but it misreads the legislative history. Earlier versions of the legislation limited estoppel to issues actually raised and decided by the PTAB. *See* Joe Matal, *A Guide to the Legislative History of the America Invents Act: Part II of II*, 21 Fed. Cir. B.J. 539, 616 (2012). After objections from patent owners, the sponsors changed the language back to the could-have-raised language of the *inter partes* reexamination statute. *Id.* at 616-17. References to enhanced or strengthened estoppel likely referred to that reversion. No committee reports or sponsor statements stated an intent to extend estoppel to prevailing parties. Janssen and the PTO observe that pre-AIA § 315(c) expressly referred to claims "finally determined to be valid and patentable," whereas § 315(e)(2) refers to a "final written decision under section 318(a)." But that change reflected the change in trigger from a final appellate decision to a final PTAB decision. Surely someone would have mentioned such a momentous and "counterintuitive" change from the traditional rule had Congress so intended. Janssen and the PTO read too much into the

rewording. *Cf. Helsinn Healthcare S.A. v. Teva Pharm. USA, Inc.*, 139 S. Ct. 628 (2019) (unanimously holding that the AIA did not alter on-sale bar's meaning despite Congress's rewording of § 102).

Janssen's interpretation should also be rejected because it would lead to absurd results. *See United States v. X-Citement Video, Inc*., 513 U.S. 64, 68-69 (1994) (courts construe even seemingly plain statutory language to avoid absurd results); *cf. Eli Lilly & Co. v. Medtronic, Inc*., 496 U.S. 661, 672-73 (1990) (rejecting interpretation of the Hatch-Waxman Act that would have enshrined "anticompetitive restriction[s]"). Although injunctions under 35 U.S.C. § 283 are discretionary and subject to equitable principles, *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391-92 (2006), orders delaying launches of generic products found to infringe are mandatory, 35 U.S.C. § 271(e)(4)(A) ("[T]he court shall order the effective date of any approval of the [generic] drug … product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed."). Janssen contends that a successful IPR petitioner must be barred from asserting invalidity over prior art and from launching an ANDA product even though—indeed precisely *because*—it has convinced the PTAB that the asserted claims were obvious over the same art. As the district court noted, under Janssen's interpretation a court would be "required to enter an injunction against infringement based on a patent already found invalid." Appx98 n.13. That cannot be right, and

Congress could not have contemplated that result when one of its "core principles" in passing the AIA was "ensur[ing] that our patent enforcement laws and procedures do not create incentives for opportunists with invalid claims to exploit." Appx14560 (statement of Rep. Goodlatte). Congress intended the AIA to make it easier to challenge suspect patents, not to penalize those who successfully do so. Moreover, Janssen's interpretation would create unnecessary tension between the courts and the PTAB and between sections of the Patent Act, contrary to the canon that statutes should be construed harmoniously.[5]

3. § 315(e)(2) estoppel did not apply during the district-court proceedings because the PTAB's decisions were not final

Even if § 315(e)(2) estoppel could apply to prevailing parties, the district court correctly concluded that no estoppel applied when it ruled because the PTAB had not finally resolved the IPRs. Appx98-99 n.13. Although the PTAB's three January

[5] *In re Certain Hybrid Vehicles and Components Thereof*, Inv. No. 337-TA-1042, at 7 n.12 (USITC I.D. Nov. 1, 2017), and *SiOnyx, LLC v. Hamamatsu Photonics K.K.*, 330 F. Supp. 3d 574, 600-01 (D. Mass. 2018), do not counsel otherwise. The former was an initial determination by an ALJ; the Commission granted review shortly thereafter, and the parties settled before the Commission ruled. In the latter, the district court assumed that the issue made no practical difference: the IPR was already on appeal, and the court reasoned that the appeal would either confirm unpatentability, rendering estoppel moot, or lead to reversal, in which case the defendants would not have prevailed. Here, the IPRs were not on appeal when the district court ruled, and Janssen's automatic-injunction theory highlights the issue's practical significance.

2018 decisions were labeled "Final Written Decision," their finality was subject to an important contingency: filing of a rehearing request.

Under PTAB rules, a party dissatisfied with a nominally final written decision may request rehearing within 30 days. 37 C.F.R. § 42.71(d). Janssen filed timely requests for rehearing. Appx30135-30151; Appx35725-35741; Appx41973-41988. Those requests meant that the PTAB had not yet rendered its final word on patentability, and they remained pending when the district court tried the case in July-August 2018 and entered judgment in October 2018. The PTAB did not finally resolve patentability until it denied rehearing in December 2018, Appx226-234; Appx298-305; Appx378-384, by which point the district-court case was on appeal.

Under § 315(e)(2), estoppel requires "a final written decision *under section 318(a)*" (emphasis added). Section 318(a) requires the PTAB to issue "a final written decision with respect to the patentability of any patent claim" at issue. Section 319, in turn, makes clear that a "final written decision ... under section 318(a)" is an *appealable* decision:

> A party dissatisfied with the *final written decision* of the Patent Trial and Appeal Board *under section 318(a)* may *appeal the decision pursuant to sections 141 through 144*.

35 U.S.C. § 319 (emphases added). Section 141(c) similarly provides that a party "dissatisfied with the final written decision" of the PTAB "may appeal" *that decision* to this Court. 35 U.S.C. § 141(c). Accordingly, the "final written decision" that

triggers estoppel under § 315(e)(2) must be an appealable decision. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1362 (2018) (Breyer, J., dissenting) (comparing the majority's reading of § 318(a) with an alternative and noting that both interpretations required the PTAB to "write a final, and *appealable*, see § 319, decision").

The requirement that a "final written decision" be the PTO's final word on patentability is consistent with longstanding principles of appellate jurisdiction. Unless Congress specifies otherwise, this Court's jurisdiction over PTAB decisions "extends only to *final* decisions" of the Board. *Bennett Regulator Guards, Inc. v. Atl. Gas Light Co.*, 905 F.3d 1311, 1315 (Fed. Cir. 2018). Parties to administrative proceedings may seek appellate review only after *final* agency action, and "[g]enerally, agency action is final when the agency's decision-making process is complete and the action determines legal 'rights or obligations' or otherwise gives rise to 'legal consequences.'" *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1361 (Fed. Cir. 2018) (citations omitted).

Here, Janssen chose to file rehearing requests that deprived the IPR decisions of finality. In so doing, Janssen reset the period for filing a notice of appeal until the requests were resolved. 37 C.F.R. § 90.3(b)(1). The rehearing requests prevented finality because the January 2018 decisions, although nominally "final," did not terminate the IPRs and did not resolve the parties' disputes. Janssen did not regard the January 2018 decisions as the PTAB's final word because it requested rehearing

rather than appealing. Janssen suggests that the PTAB's decisions were final for estoppel purposes but non-final for purposes of further consideration by the PTAB and appeal to this Court, but that would require reading the same statutory requirement, a "final written decision" "under § 318(a)," differently in two sections of the AIA. Yet "[i]t is difficult to believe that a different scope was intended to be given to the same words in different sections of the legislation." *Davies Warehouse Co. v. Bowles*, 321 U.S. 144, 150 (1944).

Janssen and the PTO note that common-law collateral estoppel may attach despite a pending rehearing request. But this statutory version expressly ties estoppel and appealability to the same "final written decision." Decisions on rehearing are not appealable and thus not "final written decisions" that can trigger statutory estoppel.

Janssen and the PTO champion the "plain language" of the statute, but they give short shrift to Congress's use of the term "final." Janssen contends that whether a PTAB ruling is final turns entirely on the title the Board chooses for a paper, but that elevates form over substance. The Supreme Court has rejected similarly rigid statutory interpretations that would produce illogical results. *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 413-16 (2012) (emphasizing that "context matters" in statutory interpretation and that "the mere possibility of clearer phrasing

cannot defeat the most natural reading of a statute"). Congress chose the word "final" when it identified the condition required for estoppel and appealability, and the term should not be read to encompass determinations still being reassessed.

Janssen points to a commentator's statement that § 315(e)(2) "appl[ies] as soon as the PTAB enters a final written decision" and its "effect is not delayed pending completion of an appeal to the Federal Circuit." But that statement merely recognized that estoppel attaches after a final decision of the *PTAB* rather than a final decision on *appeal*, without addressing what qualifies as a final PTAB decision. The PTO notes that pre-AIA § 315(c), governing *inter partes* reexamination, provided an estoppel after the challenged claims were "finally determined to be valid and patentable," which this Court held required conclusion of all appeals. But although § 315(e)(2) no longer requires conclusion of all appeals, estoppel still requires a *final* PTAB decision, which the AIA defines as the final, appealable word of the Board.

Janssen and the PTO also cite PTAB decisions involving § 315(e)(1), which limits IPR petitioners' ability to request or maintain further PTO proceedings after a final written IPR decision involving the same claims. But the supposedly seminal ruling, *Apple Inc. v. Personalized Media Commc'ns LLC*, IPR2016-01520, 2018 WL 922376, at *2 (PTAB Feb. 15, 2018), was a case in which the PTAB dismissed certain claims with no meaningful analysis after the parties *agreed* that they should be

dismissed. In any event, the PTAB's interpretations of the Patent Act are not binding, and this Court and the Supreme Court have frequently rejected them.

Finally, Janssen and the PTO argue that tying estoppel to the initial post-trial merits decision promotes speed and certainty. It does not. The PTO aims to issue post-trial decisions within twelve months of institution and rehearing decisions within two months of requests. But neither date is set in stone: the AIA targets a "final determination" "not later than 1 year after" institution, but it gives the Director six months of wiggle room and discretion to adjust in cases of joinder. 35 U.S.C. § 316(a)(11). As this case illustrates, there is no certain timeline: Amerigen filed its petition in December 2015, review was instituted in May 2016, the PTAB ruled in January 2018, and the PTAB denied rehearing in December 2018. The PTO could have designed a reconsideration-free process in which its "final determination" was always a "final written decision" under § 318(a) appealable under § 319. It instead chose a two-step system with a post-hearing merits determination a year after institution (in most cases) and another round of possible reconsideration before that decision is truly final and appealable. That was permissible, but the PTO's injection of flexibility cannot justify treating a decision subject to further agency review as the Board's "final written decision" for purposes of §§ 315(e)(2), 318(a), and 319.

4. § 315(e)(2) does not bar Appellees from defending the district court's judgment on appeal because an appeal is not "a civil action arising … under section 1338"

The PTAB ultimately denied Janssen's rehearing petitions during this appeal. In a footnote, Janssen suggests that because the PTAB proceedings are final *now*, § 315(e)(2) bars Appellees from defending the district court's invalidity judgment in this Court. Janssen again misreads the statute.

Under § 315(e)(2), an IPR petitioner may not "assert" invalidity on certain grounds "in a civil action arising in whole or in part under section 1338 of title 28." Appellees are now defending the district court's invalidity determination, not affirmatively asserting anything. Even if defending the district court's judgment were an "assertion" of invalidity, Appellees' arguments on appeal are not "in a civil action." The district-court litigation was a civil action arising under § 1338, but this appeal is not a part of that civil action and does not arise under § 1338. It is a separately docketed proceeding in a different court, and this Court has jurisdiction under 28 U.S.C. § 1295(a)(1) because the appeal is "from a final decision of [the] district court ... in a[ ] civil action" that has *concluded*.

III. The district court erred in analyzing infringement

Janssen does not argue for reversal in the PTAB cases, only for vacatur and remand. Janssen does seek reversal in the district-court case and a § 271(e)(4)(A) order revoking Appellees' FDA authorizations, but its arguments about misweighing

of the obviousness evidence would at most warrant vacatur and remand. Even if statutory estoppel barred Appellees from presenting their defense at trial, vacatur of the PTAB's final written decisions would remove the estoppel.

In any event, a § 271(e)(4)(A) order would be improper because the district court erred in finding infringement. Those errors provide an alternative ground for affirming the district court's judgment that Janssen is entitled to no relief, and they at least require a remand.

A. Janssen did not show that FDA approved prednisone to fight cancer

"For method-of-use patents, the 'artificial' infringement claim provided by section 271(e)(2)(A) lies only against a patented use that has been approved by the FDA." *Bayer Schering Pharma AG v. Lupin Ltd.*, 676 F.3d 1316, 1319 (Fed. Cir. 2012). Under the district court's construction, the patented use requires that abiraterone and prednisone independently "shrink[ ] and/or kill[ ] actual cancerous tumor cells." Appx4055. FDA did not approve that use. The district court found otherwise, but only after "wrestl[ing] with an irreducible level of ambiguity in [the] combination-therapy approval" for Zytiga. Appx130.

This Court reviews *de novo* whether FDA's approval of Janssen's Zytiga label established FDA's approval of using both abiraterone and prednisone to fight prostate cancer. *Bayer*, 676 F.3d at 1319 (affirming non-infringement judgment on the pleadings). The Court should reverse the district court's conclusion that it did. To

paraphrase *Bayer*, "[t]he FDA approved label for [Zytiga] does not indicate to physicians that the specific use claimed in the ['438] patent, i.e., producing [anti-cancer effects from *both* abiraterone and prednisone], is safe and effective. ... [Because] FDA has not approved such use ... the defendants cannot be held liable for infringement of the patent." *Id.* at 1326.

Janssen's infringement theory depended on the Zytiga label's indication that Zytiga should be used "*in combination with prednisone* for the treatment of patients with metastatic castration-resistant prostate cancer." Appx25423; Appx18964-18975 (emphasis added). According to Janssen, by approving Zytiga to fight cancer when taken "in combination with prednisone," FDA implicitly approved using prednisone to fight cancer as well.

Not so. The Zytiga indication addresses FDA's approval of that particular "drug." 21 C.F.R. § 201.57(c)(2). Zytiga contains only abiraterone. Prednisone is a separate drug with separate indications. Janssen conceded that FDA has never approved any prednisone product for shrinking or killing cancer cells. Appx18595; *see also* Appx21351. Janssen's reading of the Zytiga indication conflicts with the law, which bars FDA from approving a new use of prednisone without "adequate and well-controlled" clinical trials. 21 C.F.R. § 201.57(c)(2)(iv); *see also Bayer*, 676 F.3d at 1322-24. Critically, Zytiga's label never says that prednisone fights cancer, much less discloses clinical data showing that it does. The label's indication

language may be similar to the patent claims, but "[t]he question is not just whether instructions 'describ[e] the infringing mode'"—e.g., take abiraterone with prednisone—"but whether the instructions teach an infringing use of the device *such that* we are willing to infer from those instructions an affirmative intent to infringe the patent" by using both drugs to fight cancer. *Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015).

Appellees cannot have committed indirect infringement under the district court's construction because—consistent with prednisone's FDA-approved indication for addressing hormone deficiencies—Zytiga's label teaches only the non-infringing use of prednisone for safety, not anti-cancer efficacy. *See* Appx25426; *see also* Appx141. As FDA put it: "Prednisone has been given with abiraterone to … *provide needed glucocorticoids*," Appx23985 (emphasis added), to address "safety issues" related to abiraterone, Appx24013. FDA approved similar indications for using other cancer drugs (Taxotere® and Jevtana) "in combination with prednisone," even though in those cases prednisone is not used to fight cancer. Appx23388; Appx23410; Appx21597; Appx21600; Appx21606.

If the district court's claim construction is correct, Appellees cannot indirectly infringe as a matter of law. They will not induce infringement because Janssen failed to show that "patented use ... has been approved by the FDA." *Bayer*, 676 F.3d at 1319. And they will not contribute to infringement because using prednisone solely

for safety, as opposed to anti-cancer efficacy, is a "substantial noninfringing use" under 35 U.S.C. § 271(c).

B. At minimum, remand is required because the district court did not address direct infringement

Direct infringement is an essential predicate to a claim of indirect infringement. *Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1272 (Fed. Cir. 2004). But although direct infringement was hotly disputed, the district court's infringement analysis never addressed that threshold issue. Appx123-142.

To prove indirect infringement, Janssen had to show that both abiraterone and prednisone independently achieve anti-cancer effects when used according to the Zytiga indication. At trial and in post-trial briefing, Appellees explained that Janssen made no such showing. *See* Appx18714-18723; Appx19925-19929. The district court never found otherwise. As a result, if this Court does not affirm unpatentability/invalidity, it should remand for the district court to resolve direct infringement. *See Nazomi Commc'ns, Inc. v. ARM Holdings, PLC*, 403 F.3d 1364, 1371 (Fed. Cir. 2005) (requiring "'sufficient findings and reasoning to permit meaningful appellate scrutiny'").

In any event, this Court would at least need to remand for the district court to determine whether to stay the case pending final resolution of the IPRs. The district court need not and should not enter a § 271(e)(4)(A) order while patentability/validity remains an open issue.

CONCLUSION

This Court should affirm that the claims are unpatentable and invalid.

Dated: February 15, 2019.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Federal Circuit Rule 32(a). The body of the brief contains 13,991 words, excluding the portions exempted by Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). The brief has been prepared in a proportionally spaced typeface using Microsoft® Word 2016 and 14-point Times New Roman type.

Dated: February 15, 2019. /s/Dan L. Bagatell

Dan L. Bagatell

CERTIFICATE OF AUTHORITY AND PROOF OF SERVICE

I certify that I have the authority of Charles B. Klein, Dennies Varughese, William D. Hare, and Teresa Stanek Rea to file this document with their electronic signatures.

I further certify that I served this brief on counsel of record for all parties on February 15, 2019, via electronic mail because the Court's CM/ECF system was inaccessible at that time.

I further certify that I caused this brief to be electronically filed and served on counsel of record for all parties via the Court's CM/ECF system on February 16, 2019, after the Court provided notice that normal electronic filing service had been restored.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Dated: February 16, 2019. /s/Dan L. Bagatell

Dan L. Bagatell