Filed: June 30, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,

Petitioner

v.

JANSSEN ONCOLOGY, INC.,

Patent Owner

U.S. Patent No. 8,822,438 to Auerbach et al.

Inter Partes Review IPR2016-01332

Petition for *Inter Partes* Review of U.S. Patent No. 8,822,438

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MYL 1002	Declaration of Marc B. Garnick, MD ("Garnick Decl.")
MYL 1003	O'Donnell, A. et al., "Hormonal impact of the 17α-hydroxylase/C17,20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer," Br. J. Cancer, (90):2317–2325 (2004) ("O'Donnell")
MYL 1004	Gerber, G.S. et al., "Prostate specific antigen for assessing response to ketoconazole and prednisone in patients with hormone refractory metastatic cancer," J. Urology, 144(5):1177–9 (1990) ("Gerber")
MYL 1005	U.S. Patent No. 5,604,213, Barrie S.E. et al., "17-Substituted Steroids Useful In Cancer Treatment" ("the '213 patent")
MYL 1006	Tannock, I. et al., "Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points," J. Clinical Oncology, 14:1756–1764 (1996) ("Tannock")
MYL 1007	February 3, 2012 Office Action (excerpt from prosecution history of '438 patent)
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MYL 1009	Ryan, C.J. et al., "Abiraterone in metastatic prostate cancer without previous chemotherapy," New Eng. J. Med., 368:138–148 (2013).
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MYL 1020	Harris, K.A. et al., “Low dose ketoconazole with replacement doses of hydrocortisone in patients with progressive androgen independent prostate cancer,” J. Urology, 168:542–545 (August 2002)
MYL 1021	Oh, W.K. “Secondary hormonal therapies in the treatment of prostate cancer,” Urology, 60(Supp. 3A):87–93 (2002)
MYL 1022	Tannock, I. et al., “Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer,” N. Eng. J. Med., 351:1502–12 (2004)
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MYL 1024	Hellerstedt, B.A. et al., “The current state of hormonal therapy for prostate cancer,” CA Cancer J. Clin., 52:154–179 (2002).
MYL 1025	Kasper, D.L. et al. (Eds.), Harrison’s Principles of Internal Medicine, 16th Edition (2005), 549.

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MYL 1028	Jubelirer, S.J., et al., "High dose ketoconazole for the treatment of hormone refractory metastatic prostate carcinoma," J. Urol., 142(1):89–91 (1989)
MYL 1029	U.S. Patent 5,688,977, Sisti, N.J. et al., "Method for Docetaxel Synthesis"
MYL 1030	U.S. Food and Drug Administration ("FDA") FDA News Release dated May 19, 2004, "FDA Approves New Indication for Taxotere-Prostate Cancer"
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MYL 1040	Cancer.net (ASCO Patient Website), Treatment of Metastatic Castration-Resistant Prostate Cancer, http://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/treatment-metastatic-castration-resistant-prostate-cancer (accessed 6/28/2016).
MYL 1041	Cancer.org (ACS), “What are the key statistics about prostate cancer?” http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics (accessed 6/28/2016).
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MYL 1046	FDA Website, Drugs@FDA – Zytiga, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails (accessed 6/28/2016).
MYL 1047	FDA Website, Orange Book, Zytiga (NDA 202379), http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202379&Product_No=001&table1=OB_Rx (accessed 6/30/2016).
MYL 1048	*Galderma Labs., L.P. v. Tolmar, Inc.,* 737 F.3d 731, 740–41 (Fed. Cir. 2013).
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MYL 1050	Kirby, M. et al., "Characterising the castration-resistant prostate cancer population: A systematic review," Int'l J. Clinical Practice 65(11):1180–1192 (2011).
MYL 1051	Mayo Clinic Website, Prostate cancer, http://www.mayoclinic.org/diseasesconditions/prostate-cancer/basics/definition/con-20029597?p=1 (accessed 6/28/2016).
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MYL 1054	Murphy, W.J., J.L. Orcutt & P.C. Remus (2012), Patent Valuation: Improving Decision Making through Analysis, Hoboken, NJ: Wiley.
MYL 1055	PMLiVe Website, "Top 50 Pharmaceutical Products by Global Sales," http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales (accessed 6/30/2016).
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MYL 1064	Zytiga Brochure, Putting Prednisone in Perspective, 3/2015.
MYL 1065	Zytiga Label, 5/20/2015.
MYL 1066	Zytiga Website, How Zytiga® (abiraterone acetate) Works, https://www.zytiga.com/print/about-zytiga/how-zytiga-works (accessed 6/28/2016).
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MYL 1077	May 30, 2014 IDS (excerpt from prosecution history of ’438 patent)
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MYL 1079	Fakih, M. et al., “Glucocorticoids and treatment of prostate cancer: A preclinical and clinical review,” Urology 60:553-561 (2002)
MYL 1080	Lam, J.S. et al., “Secondary hormonal therapy for advanced prostate cancer,” J. Urology 175:28-34 (2006)

TABLE OF ABBREVIATIONS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AR	Androgen receptor
CRPC	Castration-resistant prostate cancer
mCRPC	Metastatic castration-resistant prostate cancer
CYP17	17α-hydroxylase/C17,20-lyase
DHT	Dihydrotestosterone
IDS	Information Disclosure Statement
LH	Luteinizing hormone
NDA	New Drug Application
POSA	Person of Ordinary Skill in the Art
PSA	Prostate-specific antigen
RCE	Request for Continued Examination

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") petitions for *Inter Partes* Review of claims 1-20 of U.S. Patent No. 8,822,438 to Auerbach *et al.* ("the '438 patent") (MYL Ex. 1001), which is assigned to Janssen Oncology, Inc. ("Janssen"), under 35 U.S.C. §§ 311–319 and 37 C.F.R. Part 42 and seeks a determination that all claims (1-20) of the '438 patent be canceled as unpatentable.

This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed herewith is a power of attorney and an exhibit list per § 42.10(b) and § 42.63(e), respectively. Pursuant to 37 C.F.R. § 42.103, the fee set forth in § 42.15(a) accompanies this Petition.

II. MANDATORY NOTICES

Petitioner provides the following mandatory notices.

A. Real Parties-In-Interest Under 37 C.F.R. § 42.8(b)(1)

The real parties-in-interest for Petitioner are Mylan Pharmaceuticals Inc., Mylan Inc., Mylan N.V., and Mylan LLC.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

The following litigations or instituted *inter partes* reviews related to the '438 patent are pending:

- *Amerigen Pharms. Ltd. v. Janssen Oncology, Inc.*, IPR2016-00286 (P.T.A.B.);

- *Argentum Pharms. LLC v. Janssen Oncology, Inc.*, IPR2016-01317 (P.T.A.B.).
- *BTG Int'l Ltd. v. Actavis Labs. FL, Inc.*, No. 15-cv-5909-KM-JBC (D.N.J.);
- *BTG Int'l Ltd. v. Amerigen Pharms., Inc.*, No. 16-cv-02449-KM-JBC (D.N.J.);
- *BTG Int'l Ltd. v. Glenmark Pharms. Inc., USA*, No. 16-cv-03743-KM-JBC (D.N.J.); and
- *Janssen Biotech, Inc. v. Mylan Pharms. Inc.*, No. 15-cv-00130-IMK (N.D.W. Va.).

C. Lead And Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Lead Counsel	Back-Up Counsel
Brandon M. White (Reg. No. 52,354) Perkins Coie LLP 700 Thirteenth Street, N.W. Suite 600 Washington, D.C. 20005 Telephone: (202) 654-6206 Facsimile: (202) 654-9681 bmwhite@perkinscoie.com	Bryan D. Beel (*pro hac vice to be filed*) Perkins Coie LLP 1120 NW Couch Street Tenth Floor Portland, OR 97209 Telephone: (503) 727-2116 Facsimile: (503) 346-2116 bbeel@perkinscoie.com

D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Please direct all correspondence to lead counsel and back-up counsel at the contact information above. Petitioner consents to electronic service by e-mail at

the above listed email addresses of lead and back-up counsel (bmwhite@perkinscoie.com and bbeel@perkinscoie.com).

III. GROUNDS FOR STANDING (37 C.F.R. §§ 42.101 and 42.104)

As required by 37 C.F.R. § 42.104(a), Petitioner certifies that the '438 patent is available for *inter partes* review and that the Petitioner is not barred or estopped from requesting *inter partes* review on the grounds identified herein.

IV. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED (37 C.F.R. § 42.22(a) and 37 C.F.R. § 42.104(b))

Petitioner requests *inter partes* review and cancellation of claims 1–20. Petitioner's full statement of the reasons for the relief requested is set forth below.

Petitioner respectfully requests *inter partes* review and cancellation of claims 1–20 of the '438 Patent based on the grounds set forth below:[1]

Ground 1: Claims 1-20 are unpatentable as obvious under 35 U.S.C. § 103 over O'Donnell in view of Gerber

Ground 2: Claims 1-4 and 5-11 are unpatentable as obvious under 35 U.S.C. § 103 over the '213 patent in view of Gerber.

In support of these grounds for unpatentability, Petitioner submits the expert declaration of Marc B. Garnick, M.D. (MYL Ex. 1002 ("Garnick Decl.")) and the

[1] Mylan's asserted grounds of obviousness are the same as those instituted in IPR2016-00286, filed by Amerigen Pharmaceuticals Limited.

declaration of economics expert Ivan T. Hofmann (MYL Ex. 1017 ("Hofmann Decl.")). Petitioner also relies on the other Exhibits set forth in the concurrently filed Listing of Exhibits.

V. THRESHOLD REQUIREMENT FOR INTER PARTES REVIEW

A petition for *inter partes* review must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). This Petition meets this threshold. As explained below, there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims.

VI. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

A. Summary of the Argument

The claims of the '438 patent are directed to treating prostate cancer by administering therapeutically effective amounts of abiraterone acetate, a 17α-hydroxylase/C17,20-lyase inhibitor ("CYP17 inhibitor"), in combination with prednisone, a glucocorticoid. MYL Ex. 1002, Garnick Decl. ¶¶34–35. The prior art taught the use of abiraterone acetate as an effective anti-cancer agent that suppresses testosterone synthesis in prostate cancer patients. MYL Ex. 1002, Garnick Decl. ¶¶36, 55, 66, 68. It was known as of the earliest priority date claimed by the '438 patent that testosterone promoted prostate cancer proliferation and progress, so that testosterone synthesis must be suppressed to treat prostate cancer.

However, it was also known that in using a CYP17 inhibitor to reduce testosterone synthesis, the CYP17 inhibitor undesirably suppressed the production of cortisol, a glucocorticoid, which is necessary for other biochemical cycles in the body. In particular, reduced production of cortisol caused adverse effects, including hypertension, hypokalemia (decrease in circulating potassium levels), and fluid retention. To address the suppressed synthesis of cortisol, the prior art taught that concomitant glucocorticoid replacement therapy might be necessary when administering abiraterone to treat prostate cancer in a patient, and that this was common practice in the treatment of prostate cancer with ketoconazole, another CYP17 inhibitor. MYL Ex. 1002, Garnick Decl. ¶¶42, 44, 58.

The prior art also taught that abiraterone was a more effective CYP17 inhibitor than ketoconazole. For example, the prior art taught that abiraterone acetate was more effective in decreasing testosterone levels in a mammal than ketoconazole. MYL Ex. 1002, Garnick Decl. ¶¶46, 55. The prior art also taught that the combination of ketoconazole and prednisone was a safe and effective treatment for refractory metastatic prostate cancer. MYL Ex. 1002, Garnick Decl. ¶58.

One of skill in the art would have combined abiraterone acetate and prednisone based on the teachings of O'Donnell in view of Gerber, and/or the '213 patent in view of Gerber, for a safe and effective treatment of prostate cancer with

a reasonable expectation of success. The prior art taught that abiraterone acetate was a more effective CYP17 inhibitor than ketoconazole and that the combination of ketoconazole and prednisone was safe and effective to treat patients with hormone refractory metastatic prostate cancer, which would have motivated the combination. MYL Ex. 1002, Garnick Decl. ¶¶55–59. One of skill in the art may also have been motivated by prednisone's possible anti-cancer effects. *Id.* ¶ 89.

There are no secondary considerations of commercial success that overcome this case of obviousness. The claims of the application that resulted in the '438 patent were repeatedly rejected for obviousness until the Examiner allowed the claims based on the purported "unexpected commercial success" of Zytiga, the brand name under which abiraterone acetate is marketed in the United States by the Assignee. In particular, the Examiner's allowance of the claims based on secondary considerations of commercial success of Zytiga was in error because Applicants failed to show the necessary nexus between the claimed invention (which is directed to a method of treating prostate cancer by administering abiraterone acetate and prednisone) and any commercial success of the drug Zytiga.

B. Level of Ordinary Skill in the Art

A person of ordinary skill in the art is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary

creativity. With respect to the '438 patent, the scientific field relevant is oncology or urology. MYL Ex. 1002, Garnick Decl. ¶18. A person of ordinary skill in the art would be a physician specializing in urology, endocrinology, or oncology, or a person holding a Ph.D. in pharmacology, biochemistry or a related discipline, such as pharmaceutical science. MYL Ex. 1002, Garnick Decl. ¶18. Additional experience could substitute for the advanced degree. MYL Ex. 1002, Garnick Decl. ¶18. To the extent necessary, one of skill in the art may collaborate with one or more other persons of skill in the art for one or more aspects with which the other person may have expertise, experience and/or knowledge that was obtained through his or her education, industrial or academic experiences. MYL Ex. 1002, Garnick Decl. ¶19. For example, one of skill may consult with an endocrinologist, oncologist, or medical biochemist and thus may rely on the opinions of such specialists in evaluating the claims. MYL Ex. 1002, Garnick Decl. ¶20.

C. U.S. Patent No. 8,822,438 and Its File History

1. Specification of the '438 Patent

The "Background" section of the '438 patent describes prostatectomy and radiotherapy, a primary course of treatment for patients diagnosed with organ-confined prostate cancer, as being highly invasive and ineffective on metastasized prostate cancer. MYL Ex. 1001, col. 1, ll. 25–32. In addition, the specification states that these localized treatments are not effective on prostate cancer after it has

metastasized and that, moreover, a large percent of individuals who receive such localized treatments will suffer from "recurring cancer." *Id.* at ll. 28–33. The specification states that another treatment option for prostate cancer, hormone therapy, is less invasive than surgery and has fewer side effects. *Id.* at ll. 43–44, 51–53. However, the specification notes that hormone therapy is not equally effective in all patients thus treated, and some patients suffer from relapsing or recurring cancer after hormone therapy. *Id.* at ll. 57-64.

The "Summary of the Invention" section of the '438 patent describes various embodiments of the invention as being directed to methods and compositions of treating a refractory cancer in a patient, involving administering an effective amount of a CYP17 inhibitor and an effective amount of another anticancer agent such as mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, flutamide, or a steroid including prednisone or dexamethasone. MYL Ex. 1001, col. 2, l. 9 – col. 3, l. 20.

The "Definitions" section defines "17α-hydroxylase/C17,20-lyase inhibitor" as an inhibitor of the enzyme "17α-hydroxylase/C17,20-lyase" (an enzyme involved in testosterone synthesis). MYL Ex. 1001, col. 3, l. 66 – col. 4, l. 7. The terms "treat," "treating" and "treatment" are defined 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." MYL Ex. 1001, col. 3, ll. 46–50. The term "anti-cancer agent" is defined as "any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits stops or reduces the proliferation of cancer cells." MYL Ex. 1001, col. 4, ll. 8–16. The term "refractory cancer" is defined as "cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment." MYL Ex. 1001, col. 4, ll. 23–27.

The "Detailed Description of the Invention" section refers to U.S. Patent No. 5,604,213 (MYL Ex. 1005) for its disclosure of CYP17 inhibitors being "shown to be useful in the treatment of cancer, specifically hormone-dependent disorders such as, androgen-dependent and estrogen-dependent disorders like prostate cancer and breast cancer." MYL Ex. 1001, col. 5, ll. 23–29. The specification provides a list of various CYP17 inhibitors including abiraterone (17-(3-pyridyl)-androsta-5,16-diene-3β-ol). MYL Ex. 1001, col. 5, ll. 30–40.

According to the specification, the CYP17 inhibitors may also be administered or combined with steroids, such as corticosteroids or glucocorticoids including hydrocortisone, prednisone, or dexamethasone, in the same or different compositions. MYL Ex. 1001, col. 10, ll. 15–21. A single-unit solid oral dosage form may contain about 50 mg to about 300 mg of abiraterone acetate and about 0.5 to 3 mg of a steroid, *e.g.*, glucocorticoid, optionally with additional excipients. MYL Ex. 1001, col. 10, ll. 42–50. Suitable daily dosages of CYP17 inhibitors

according to the ’438 patent can generally range from about 0.0001 mg/kg/day to about 1000 mg/kg/day. MYL Ex. 1001, col. 11, ll. 33–43.

According to the specification, the method for the treatment of cancer can comprise administering an amount of about 50 mg/day to about 2000 mg/day or about 500 mg/day to about 1500 mg/day of abiraterone acetate, and an amount of about 0.01 mg/day to about 500 mg/day or about 0.5 mg/day to about 25 mg/day of glucocorticoid, such as hydrocortisone, dexamethasone or prednisone. MYL Ex. 1001, col. 13, ll. 6–39.

One example of a composition according to the invention comprises a CYP17 inhibitor such as abiraterone acetate in combination with a steroid, such as hydrocortisone, prednisone or dexamethasone. The composition can comprise about 50–500 mg of abiraterone acetate, and about 0.25–3.5 mg of steroid. MYL Ex. 1001, col. 15, ll. 52–55.

2. File History of the ’438 Patent

The ’438 patent has a lengthy and involved prosecution. The application resulting in the ’438 Patent was filed on February 24, 2011, and assigned Application No. 13/034,340. MYL Ex. 1001, cover page ¶¶(21), (22). The application was filed as a continuation of Application No. 11/844,440, filed on August 24, 2007, which claims priority to Provisional Application No. 60/921,506, filed on August 25, 2006. *Id.* ¶¶(60), (63).

In an Office Action dated November 25, 2011, the Examiner imposed restriction between the claims of Group I (claims 1–26, drawn to a method for treating cancer), and the claims of Group II (claims 27–36, drawn to a composition). MYL Ex. 1068, November 25, 2011, Office Action at 2. In a Response dated December 21, 2011, Applicants cancelled the pending claims, and elected the invention of Group I, represented by newly-presented claims 37–56. MYL Ex. 1069, December 21, 2011, Response at 1–5. Newly-presented claims 37–56 are substantively similar to claims 1–20 of the '438 patent as issued.

In an Office Action dated February 3, 2012, all pending claims (*i.e.*, 37–56) were rejected for obviousness over O'Donnell (MYL Ex. 1003) in view of Tannock (MYL Ex. 1006). MYL Ex. 1007, February 3, 2012 Office Action, at 2. The Examiner characterized O'Donnell as disclosing the CYP17 inhibitor abiraterone acetate being used to suppress testosterone levels in prostate cancer patients. *Id.* Tannock was cited for teaching "10 mg of prednisone in combination with other anit-cancer [*sic*] drug [*i.e.*, mitoxantrone] as effective in treating refractory hormonal-resistance [*sic*] prostate cancer." MYL Ex. 1007 at 3.

In a Response dated July 3, 2012, Applicants argued that "[n]othing in the art teaches or suggests that abiraterone acetate in combination with prednisone would be a particularly useful combination for cancer treatment." July 3, 2012 Response (MYL Ex. 1008) at 2. Applicants further argued that "[e]ven if one of

ordinary skill would have been motivated to combine both modes of treatment, the claimed invention produces unexpected results." *Id.*

As alleged evidence in support of unexpected results, Applicants cited Sartor, Nature Reviews Clinical Oncology, 8:515–516 (2011), reporting data from a clinical study of patients with metastatic castration-resistant prostate cancer ("mCRPC") previously treated with chemotherapy who were treated with the combination of abiraterone and prednisone or prednisone alone. *Id.* Applicants described Sartor as teaching that "[a]biraterone plus prednisone prolongs overall survival relative to prednisone alone." MYL Ex. 1008 at 2.

Applicants also argued that worldwide sales data for Zytiga (the trade name under which abiraterone acetate is marketed) were evidence of purported commercial success of the claimed invention. *Id.* at 3. According to the Applicants, sales of Zytiga were evidence of the commercial success of the claimed combination because the approved label for Zytiga directs patients to use Zytiga in combination with prednisone. *Id.*

In a Final Office Action dated September 11, 2012, the Examiner maintained the rejection of the claims over O'Donnell and Tannock. MYL Ex. 1070, September 11, 2012, Office Action at 2–4. In a Request for Continued Examination ("RCE") and Response dated January 11, 2013, Applicants once again argued unexpected results and cited Ryan *et al.*, New Eng. J. of Med.,

368:138–148 (2013) (MYL Ex. 1009), purporting to show unexpected results of the claimed invention over prednisone. MYL Ex. 1010 at 6. For example, Applicants argued an "unexpected survival benefit of abiraterone in combination with prednisone" over "prednisone alone." MYL Ex. 1010, January 11, 2013 Response at 7; MYL Ex. 1002, Garnick Decl. ¶77.

In a Final Office Action dated March 4, 2013, the Examiner continued to maintain the obviousness rejection of claims 37–56 over O'Donnell and Tannock. MYL Ex. 1011, March 4, 2013 Office Action at 2. The Examiner explained that "[s]ince abiraterone acetate provide a new mechanism of action in treating prostate cancer and prednisone is known to be useful in treating refractory prostate cancer, concomitant employment of both compounds into a single method useful for the very same purpose, treating prostate cancer, would be considered *prima facie* obvious." *Id.*

However, as explained in the Garnick Declaration, the Examiner's stated reasons for combining both compounds into a single method included incorrect facts. First, abiraterone acetate did not provide a new mechanism of action. As explained above and set out in O'Donnell, both ketoconazole and abiraterone were known CYP17 inhibitors acting by the same mechanism. MYL Ex. 1002 (Garnick Declaration) ¶¶33, 36. Second, prednisone was not accepted as being useful for treating cancer. As explained in the Garnick Declaration, MYL Ex. 1002, Garnick

Decl. ¶¶83-84, 89, 90, although there was a belief that prednisone might be useful for treating prostate cancer, at the time of filing of the '438 patent, prednisone's use as an effective anti-cancer agent for prostate cancer was much less clear than its use as a palliative agent. It was therefore common practice to co-administer a glucocorticoid such as prednisone with a CYP17 inhibitor for glucocorticoid replacement. MYL Ex. 1002, Garnick Decl. ¶¶44, 58, 78.

In a Notice of Appeal and Response dated June 4, 2013, Applicants reiterated their argument that Tannock purportedly taught away from the use of prednisone with abiraterone acetate because Tannock taught that "[t]here was no significant difference in overall survival [between prednisone alone and prednisone plus the anti-cancer agent mitoxantrone]." Response dated June 4, 2013 (MYL Ex. 1012) at 6 (brackets in original). Applicants argued that one of skill in the art, reading Tannock, would have expected "there to be no difference in survival between one cancer agent alone, and that same cancer agent in combination with prednisone." MYL Ex. 1012 at 6.

Applicants also provided the FDA approval label for Zytiga and argued that "[t]aking Zytiga in accordance with the approved label [*i.e.*, in combination with prednisone] represents a commercial embodiment of the presently claimed invention." MYL Ex. 1012 at 7. Applicants also submitted a news release from FDA announcing that Zytiga was approved for the additional indication "for use in

prostate cancer patients prior to receiving chemotherapy" and argued that this provided additional evidence of commercial success of the claimed combination. MYL Ex. 1012 at 7.

Applicants once again argued commercial success, this time based on market share data for Zytiga, and a Janssen-created presentation entitled "Pharmaceuticals Commercial Overview" by Joaquin Duato, Worldwide Chairman, Pharmaceuticals, Janssen, dated May 2013 ("Duato presentation"), which characterized Zytiga as having the most successful launch of an oral oncology product ever: "Zytiga®: Most Successful Oral Oncology Launch in History." MYL Ex. 1012 at 7; *id.* at Exhibit page 40 (slide 11).

Applicants specifically pointed to a slide showing a 70% market share for Zytiga in July 2012 for "chemo refractory prostate cancer patients." MYL Ex. 1012 at 7. Applicants argued that the Duato presentation showed that "[d]espite another product, Xtandi, being introduced in August of 2012, by April of 2013, Zytiga was still the market leader as of April 2013 with 57% market share in chemorefractory prostate cancer patients." MYL Ex. 1012 at 7-8. Applicants concluded that "not only is ZYTIGA the most successful oral oncology launch in history, two years after its initial approval it is still the market leader for chemo refractory patients despite an earlier introduced therapy [*i.e.*, Jevtana®] and a later introduced therapy [*i.e.*, Xtandi®]." MYL Ex. 1012 at 8. Applicants argued that

"[t]his commercial success [of Zytiga] demonstrates the non-obviousness of the presently claimed invention." MYL Ex. 1012 at 8.

In a Notice of Allowability dated July 3, 2013, all pending claims were allowed with the Examiner providing the following reason for allowance: "The *unexpected commercial success* of the launch of the drug obviates the rejection under 35 USC 103(a)." MYL Ex. 1013, Notice of Allowability dated July 3, 2013 at 2 (emphasis added).

In a pair of Information Disclosure Statements ("IDS") dated October 3, 2013, submitted with an RCE, Applicants provided a number of non-patent literature documents.[2] MYL Exs. 1071-72. Among the references listed in the October 3, 2013 IDS was Gerber (MYL Ex. 1004). MYL Ex. 1071 at 3 (Item No. 17). A second Notice of Allowability issued October 25, 2013, with the Examiner stating in the Notice that the reasons for allowance were "essentially the same" as in the previous notice. MYL Ex. 1014 at 2.

Another IDS submitted with a second RCE and listing additional non-patent documents was filed by Applicants on January 10, 2014. MYL Ex. 1073. A third

[2] In all, in the ten months *after* receiving their first Notice of Allowability for the '438 patent, the Applicants submitted seven Information Disclosure Statements to the Patent Office listing 95 newly-cited references. Applicants did not submit any Information Disclosure Statements before allowance.

Notice of Allowability issued on February 11, 2014. MYL Ex. 1015. The Examiner again stated in the Notice of Allowability that the reasons for allowance were "essentially the same as the notice of allowance mailed 7/30/2013," and further that "[t]he commercial success of the combination of prednisone and abiraterone to treat prostate cancer obviate the rejection under 35 USC 103(a)." MYL Ex. 1015 at 2.

A second pair of IDSes, dated May 9, 2014, listed a number of additional references. MYL Exs. 1074-75. These IDSes provided statements of opposition filed in the European Patent Office for a counterpart foreign application of the '438 patent; Applicants' response to the opposition; and a number of additional references. *See, e.g.*, MYL Ex. 1075. Additional Information Disclosure Statements filed on May 30, 2014, provided more of the same. MYL Exs. 1076-77. A fourth Notice of Allowance issued on June 2, 2014, reiterating the same grounds for allowance as the previous notice. MYL Ex. 1016.

D. Claim Construction (37 C.F.R. §§ 42.100(b), 42.104(b)(3))

Pursuant to 37 C.F.R. § 42.100(b), a claim in an unexpired patent is given its broadest reasonable interpretation in light of the specification. *Cuozzo Speed Techs., LLC v. Lee*, No. 15-446, 2016 WL 3369425 (U.S. June 20, 2016). Petitioner submits for purposes of this petition only that the terms in the claims of the '438 patent do not have any special meanings and are presumed to take on their

broadest reasonable meaning consistent with the understanding of a person of ordinary skill in the art ("POSA") when read in light of the '438 patent's specification. Because the claim construction standard in an *inter partes* review is different than that used in litigation, Petitioner reserves the right to present different constructions of terms in litigation under claim construction standards appropriate for those cases. *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1369 (Fed. Cir. 2004).

The following terms in the claims of the '438 patent should be construed for purposes of this petition as they are defined in the specification of the '438 patent; the Board adopted each of these constructions in the Institution Decision (Paper No. 14) in IPR2016-00286:

- The terms "treat," "treating" and "treatment" should be construed to mean: "***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." MYL Ex. 1001, col. 3, ll. 46–50 (emphasis added).[3]

[3] In its co-pending district court litigation, Petitioner argues that "treat," "treating," and "treatment," properly construed, encompass both palliative and anti-cancer effects, consistent with the Board's claim construction in the institution decision in IPR2016-00286. *See BTG Int'l Ltd. v. Actavis Labs. FL, Inc.*, No. 15-cv-5909-

- The term "anti-cancer agent" should be construed to mean: "any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits, stops or reduces the proliferation of cancer cells." MYL Ex. 1001, col. 4, ll. 8–16.
- The term "refractory cancer" should be construed to mean: "cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment." MYL Ex. 1001, col. 4, ll. 23–27.

See also MYL Ex. 1002, Garnick Decl. ¶¶47-53.

E. Scope and Content of the Prior Art

1. Overview

The '438 patent has a single independent claim that is directed to a method for treating prostate cancer comprising administering therapeutically effective amounts of abiraterone acetate, a CYP17 inhibitor, in combination with prednisone, a glucocorticoid. MYL Ex. 1001, claim 1; MYL Ex. 1002, Garnick Decl. ¶54; MYL Ex. 1017, Hofmann Decl. ¶19. However, the prior art taught use of abiraterone acetate as an effective anti-cancer agent that suppresses testosterone synthesis in prostate cancer patients. MYL Ex. 1002, Garnick Decl. ¶¶36, 37, 46, 55. The prior art also taught that concomitant glucocorticoid replacement therapy

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KM-JBC (D.N.J.), ECF No. 207 at 2.

might be necessary when administering abiraterone to treat prostate cancer in a patient, and that this was common practice in the treatment of prostate cancer with ketoconazole, another CYP17 inhibitor. MYL Ex. 1002, Garnick Decl. ¶¶58, 66, 78.

The prior art also taught that abiraterone was a more effective CYP17 inhibitor than ketoconazole. For example, the prior art taught that abiraterone acetate was more effective in decreasing testosterone levels in a mammal than ketoconazole. MYL Ex. 1002, Garnick Decl. ¶¶46, 55, 59. The prior art also taught that the combination of ketoconazole and prednisone was a safe and effective treatment for refractory metastatic prostate cancer. MYL Ex. 1002, Garnick Decl. ¶¶45, 58.

One of skill in the art would have combined abiraterone acetate and prednisone based on the teachings of O'Donnell and Gerber and/or the '213 patent and Gerber for a safe and effective treatment of prostate cancer with a reasonable expectation of success because the prior art taught the combination of ketoconazole and prednisone as safe and effective to treat patients with hormone refractory metastatic prostate cancer. MYL Ex. 1002, Garnick Decl. ¶¶58–59.

During prosecution, after numerous rejections for obviousness, the Applicants argued that unexpected results rebutted the *prima facie* case of obviousness made by the Examiner. The Applicants argued that the cited prior art

did not teach or suggest that "abiraterone acetate in combination with prednisone would be a particularly useful combination for cancer treatment." MYL Ex. 1008 at 2. They further argued that commercial success of Zytiga was evidence of non-obviousness of the claimed combination. MYL Ex. 1008 at 3.

However, Gerber taught that some patients with hormone refractory metastatic prostate cancer could derive significant benefit from treatment with ketoconazole and prednisone. MYL Ex. 1002, Garnick Decl. ¶45. Indeed, the administration of ketoconazole in combination with a glucocorticoid such as prednisone or hydrocortisone was a common practice at the time of the invention. MYL Ex. 1002, Garnick Decl. ¶¶41–42, 44, 78. The Examiner did not consider Gerber during prosecution. Quite possibly, this is because Gerber was submitted after the initial notice of allowance, along with dozens of other references.

Because the Examiner did not consider Gerber, the Examiner did not fully appreciate the obviousness of combining a CYP17 inhibitor (such as abiraterone) with a glucocorticoid (such as prednisone).

Applicants also argued that abiraterone and prednisone unexpectedly prolonged overall survival relative to prednisone alone, and that the prior art taught away from combining abiraterone with prednisone. MYL Ex. 1012 at 6. For example, in traversing repeated obviousness rejections over Tannock (MYL Ex. 1006), the Applicants argued that Tannock taught away from use of abiraterone

with prednisone because it showed that there "was no significant difference in overall survival [between prednisone alone and prednisone plus the cancer agent mitoxantrone]," which would have led one of skill in the art to expect "no difference in survival between one cancer agent alone, and that same cancer agent in combination with prednisone." MYL Ex. 1012 at 6 (brackets in original).

This was an erroneous and misleading inference to make for at least two reasons: (i) the co-administration of prednisone with abiraterone was not intended to enhance the anti-cancer properties of abiraterone, already known in the art to be a very selective CYP17 inhibitor (and consequently a potent inhibitor of peripheral testosterone production), but rather to reduce side effects associated with administering abiraterone; and (ii) the proper comparison for overcoming obviousness over the prior art should have been whether there was any unexpected synergistic anti-cancer benefit of using abiraterone in combination with prednisone, beyond the anti-cancer effect of administering *abiraterone* alone.

While the Examiner did not find Applicants' arguments regarding unexpected results persuasive, the Examiner also did not fully appreciate the obviousness of the claimed invention or the reason that the clamed invention does not produce unexpected results. For example, in a Final Rejection dated March 4, 2013 maintaining an obviousness rejection of the pending claims, the Examiner explained that "[s]ince abiraterone acetate provide a new mechanism of action in

treating prostate cancer and prednisone is known to be useful in treating refractory prostate cancer, concomitant employment of both compounds into a single method useful for the very same purpose, treating prostate cancer, would be considered prima facie obvious." MYL Ex. 1011 at 3. However, as explained below, CYP17 inhibitors were known in the art for treating prostate cancer, so that the mechanism of action of abiraterone acetate was not new. Additionally, it was known that co-administering a glucocorticoid such as prednisone with a CYP17 inhibitor was necessary as hormone replacement therapy in order to reduce potential side effects of administering a CYP17 inhibitor, not to enhance an anti-cancer benefit.

Moreover, the Examiner committed error in allowing the claims based on the purported "unexpected commercial success" of Zytiga, the name under which abiraterone acetate is marketed in the United States by the Assignee. In particular, the Examiner's allowance of the claims based on secondary considerations of commercial success of Zytiga was in error because Applicants failed to show the necessary nexus between the claimed invention (which is directed to a method of treating prostate cancer by administering abiraterone acetate and prednisone) and any commercial success of the drug Zytiga, which consists solely of abiraterone acetate.

2. Background of Prostate Cancer and Its Treatment

Prostate cancer is an androgen-dependent disease. MYL Ex. 1002, Garnick Decl. ¶23. The activation of androgen receptors ("AR") on prostate cells regulates the transcriptional activation of a wide variety of genes involved in promoting the progression and proliferation of prostate cancer. MYL Ex. 1002, Garnick Decl. ¶24. The two most important androgens responsible for activating the AR are testosterone and its derivative dihydrotestosterone ("DHT"). MYL Ex. 1002, Garnick Decl. ¶24.

Testosterone is synthesized primarily in the testes and the adrenals. MYL Ex. 1002, Garnick Decl. ¶24. The treatment options for treating prostate cancer depend to a great extent on whether the prostate cancer is confined or localized to the prostate or whether it has spread to other organs (*i.e.*, metastasized) from the prostate. MYL Ex. 1002, Garnick Decl. ¶25. The goal of treating primary prostate cancer (*i.e.*, prostate cancer localized to the prostate) is to interfere with the proliferation of prostate cancer cells by interrupting production of testosterone and DHT in the testes, or interfering with their function of binding with receptors on prostate cancer cells. MYL Ex. 1002, Garnick Decl. ¶25. However, a significant number of patients do not respond to localized therapy to suppress testosterone, and consequently develop metastatic prostate cancer. MYL Ex. 1002, Garnick Decl. ¶¶26–27.

The treatment of metastatic prostate cancer requires systemic therapy. MYL Ex. 1002, Garnick Decl. ¶28. An important goal in treating metastatic prostate cancer patients who have undergone localized androgen ablation is to reduce baseline circulating testosterone levels. MYL Ex. 1002, Garnick Decl. ¶28-29. A substantial amount of extratesticular testosterone is produced in the adrenal glands. MYL Ex. 1002, Garnick Decl. ¶28-29. The first-line treatment for metastatic prostate cancer patients since at least the 1980s has involved systemic suppression of extratesticular testosterone production by the peripheral organs, including the adrenal gland, and is commonly referred to as hormone therapy. MYL Ex. 1002, Garnick Decl. ¶28.

In almost all cases, patients with metastatic prostate cancer develop what is referred to as refractory or castration-resistant prostate cancer ("CRPC"), *i.e.*, prostate cancer that does not respond to a reduction in testosterone levels by surgical or chemical means and resumes growth. MYL Ex. 1002, Garnick Decl. ¶31.

The treatment of metastatic refractory prostate cancer typically also comprises the use of secondary hormone therapy to further reduce testosterone production, usually in combination with anti-androgen therapy. MYL Ex. 1002, Garnick Decl. ¶32.

CYP17 inhibitors were known in the art to be useful in the treatment of androgen-dependent cancers, including prostate cancer, by contributing to suppression of peripheral androgen production. MYL Ex. 1002, Garnick Decl. ¶¶36, 43. Ketoconazole, a non-specific inhibitor of 17α-hydroxylase, an enzyme critical to steroid synthesis, was commonly used off-label in combination with prednisone as a second-line treatment for metastatic refractory prostate cancer at the time of the invention of the '438 patent. MYL Ex. 1002, Garnick Decl. ¶33.

Like ketoconazole, abiraterone is a CYP17 inhibitor. MYL Ex. 1003, (O'Donnell) at 3-4; MYL Ex. 1002, Garnick Decl. ¶¶36, 55. CYP17 inhibitors were known to inhibit CYP17, an enzyme that is critical to androgen synthesis in both the testes and the adrenal cortex. MYL Ex. 1002, Garnick Decl. ¶37. While the CYP17 enzyme is essential for androgen biosynthesis, it also plays an important role in the production of cortisol, a glucocorticoid that is critical to basic metabolic functions including the formation of glucose, cardiovascular function, and the activation of the anti-stress and inflammatory pathways. MYL Ex. 1002, Garnick Decl. ¶38.

When a CYP17 inhibitor is administered to suppress androgen synthesis, as an undesired side effect cortisol production is compromised (*e.g.*, reduced), which interferes with the negative feedback mechanism that usually maintains cortisol levels within the normal physiological range. MYL Ex. 1002, Garnick Decl. ¶¶39–

40. This results in the pituitary gland producing more adrenocorticotropic hormone ("ACTH") to stimulate greater production of glucocorticoids, which are formed from ACTH, in part, by a reaction involving CYP17. MYL Ex. 1002, Garnick Decl. ¶40. However, in the presence of a CYP17 inhibitor, the conversion in the CYP17 pathway from ACTH to cortisol cannot occur. MYL Ex. 1002, Garnick Decl. ¶40.

It was known that CYP17 inhibition of cortisol increased ACTH drive (*i.e.*, increased ACTH production), which resulted in a corresponding increase in mineralocorticoids. MYL Ex. 1002, Garnick Decl. ¶41. An increase in mineralocorticoids beyond normal levels, known as "mineralocorticoid excess," was known to have adverse effects, including hypertension, hypokalemia (decrease in circulating potassium levels), and fluid retention. MYL Ex. 1002, Garnick Decl. ¶41. It was general knowledge in the art to administer a glucocorticoid, such as prednisone or hydrocortisone, to a patient with ACTH drive, such as a patient administered a CYP17 inhibitor, to reduce ACTH drive, and consequently, reduce mineralocorticoid excess. MYL Ex. 1002, Garnick Decl. ¶42. Therefore, in a patient being treated for prostate cancer with a CYP17 inhibitor such as ketoconazole, a patient would have been concomitantly administered a glucocorticoid such as prednisone for the purpose of reducing the side effects

associated with increased ACTH drive that result from the CYP17 inhibitor, rather than treating prostate cancer itself. MYL Ex. 1002, Garnick Decl. ¶44.

It was known that administration of ketoconazole resulted in adverse side effects including high blood pressure, hypokalemia and swelling associated with ACTH drive and mineralocorticoid excess. MYL Ex. 1002, Garnick Decl. ¶44. Therefore, it was standard practice in the art to co-administer a glucocorticoid when using ketoconazole to treat patients with refractory metastatic prostate cancer. MYL Ex. 1002, Garnick Decl. ¶44.

One of skill in the art would have expected that administering abiraterone, an even more potent inhibitor of CYP17 than ketoconazole, to treat prostate cancer in a patient might also require co-administration of a glucocorticoid, such as prednisone. MYL Ex. 1002, Garnick Decl. ¶¶79-80. One of skill in the art would therefore have appreciated that the co-administration of prednisone with abiraterone was not intended to enhance the clinically-relevant anti-cancer effect of abiraterone. MYL Ex. 1002, Garnick Decl. ¶¶83-84. Instead, 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. MYL Ex. 1002, Garnick Decl. ¶44.

3. Prior Art References

a. In 2004, O'Donnell Described the Administration of Abiraterone Acetate as More Effective for Treating Metastatic Refractory Prostate Cancer than Ketoconazole, and Possibly Requiring Concomitant Glucocorticoid Replacement Therapy

O'Donnell, A. *et al.*, "Hormonal impact of the 17α-hydroxylase/C17,20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer," Brit. J. Cancer, 90:2317–2325 (2004) (MYL Ex. 1003), published on May 18, 2004. O'Donnell is prior art to the '438 patent under at least 35 U.S.C. § 102(b) (pre-AIA) because it was published on May 18, 2004, more than one year prior to August 25, 2006, the earliest effective filing date for the claims of the '438 patent.

O'Donnell taught that abiraterone acetate is a CYP17 inhibitor that suppresses testosterone synthesis in patients with prostate cancer. MYL Ex. 1003, O'Donnell, at Abstract. O'Donnell reported that repeated treatment of male patients with prostate cancer with intact gonadal function (testicular function) with abiraterone acetate at a dose of 500–800 mg can successfully suppress testosterone levels to the castrate range. *Id.* O'Donnell also taught that the dose of abiraterone acetate administered to a particular patient may need to be adjusted in order to attain suppression of testosterone levels at target levels. *See, e.g.*, MYL Ex. 1003, O'Donnell, at Abstract, 2324. O'Donnell also reported that adrenocortical

suppression (*i.e.*, suppression of cortisol) may necessitate concomitant administration of replacement glucocorticoid with abiraterone acetate. *Id.*

O'Donnell reported that as much as 10% of baseline circulating testosterone remains in castrated men due to peripheral conversion of adrenal steroids (DHEA and androstenedione) to testosterone. MYL Ex. 1003 at 2317. O'Donnell explained that this baseline circulating testosterone can activate overexpressed androgen receptors in hormone-refractory tumors. MYL Ex. 1003 at 2317.

O'Donnell also described ketoconazole as an inhibitor of CYP17 that has shown anti-cancer activity for prostate cancer by decreasing the production of adrenal steroids. MYL Ex. 1003 at 2318. O'Donnell also described abiraterone acetate as a more selective CYP17 inhibitor than ketoconazole of the CYP17 enzyme, which will more effectively decrease the production of adrenal steroids. *Id.* O'Donnell further reported that the activity of ketoconazole as a second-line agent in clinical trials among patients with prostate cancer supports the concept of a more selective inhibitor of the CYP17 enzyme. *Id.*

O'Donnell described the potential utility of abiraterone acetate as an effective anti-cancer agent for treating both castrate and non-castrate patients with advanced prostate cancer. O'Donnell reported the results of three separate Phase I studies in which human patients with advanced prostate cancer, including patients who had progressed despite prior hormone and antiandrogen therapy, were treated

with 500–800 mg abiraterone acetate and maintained testosterone suppression at target levels. MYL Ex. 1003 at 2318-19, 2322–23.

In one study, a single-dose study in surgically or medically castrate male patients with advanced prostate cancer, a dose of 500 mg of abiraterone acetate was considered necessary to suppress testosterone to target levels. MYL Ex. 1003 at 2320.

In a second study, a single-dose study involving non-castrate male patients with advanced prostate cancer, there appeared to be a steep dose-response relationship. O'Donnell reported that at a dose of 500 mg of abiraterone acetate, treated patients showed persistent reductions in testosterone levels. MYL Ex. 1003 at 2323.

In a third, multi-dose study involving non-castrate male patients with advanced prostate cancer, O'Donnell reported that a dose of at least 800 mg was required to maintain testosterone suppression at target levels. MYL Ex. 1003 at 2323.

In addition, O'Donnell reported that repeated treatment of non-castrate patients with advanced metastatic prostate cancer with abiraterone acetate at a dose of 800 mg/day can successfully suppress testosterone levels to the castrate range. MYL Ex. 1003 at 2320–2322.

O'Donnell further reported that from the repeat-dose studies, it can be seen that a dose of at least 800 mg is required to maintain testosterone suppression at target levels in these patients. MYL Ex. 1003 at 2323.

O'Donnell also reported that adrenocortical suppression (*i.e.*, the suppression of androgens secreted in the adrenal cortex) may necessitate concomitant administration of replacement glucocorticoid. MYL Ex. 1003 at 2323. In particular, O'Donnell reported that "[a]lthough baseline cortisol levels remained normal, all patients treated at 500 and 800 mg in the multiple dose study developed an abnormal response to a short Synacthen test by Day 11," indicating a decrease in cortisol level. MYL Ex. 1003 at 2323. O'Donnell further noted that "some impact on cortisol levels was expected from the effect of abiraterone acetate on the steroid synthesis pathway." MYL Ex. 1003 at 2323. O'Donnell further disclosed that in the clinical use of ketoconazole, "it is common practice to administer supplementary hydrocortisone and this may prove necessary with … abiraterone acetate." MYL Ex. 1003 at 2323. On the basis of the clinical evidence, O'Donnell reported that the need for concomitant therapy of abiraterone acetate with a glucocorticoid needed to be investigated further. MYL Ex. 1003 at 2323.

b. In 1990, Gerber Disclosed the Use of Ketoconazole with Prednisone, a Glucocorticoid, in Patients with Hormone Refractory Metastatic Prostate Cancer

Gerber G.S. *et al.*, "Prostate specific antigen for assessing response to ketoconazole and prednisone in patients with hormone refractory metastatic prostate cancer," J. Urol., 144:1177–9 (November 1990) (MYL Ex. 1004), published in November 1990. Gerber is prior art to the '438 patent under at least 35 U.S.C. § 102(b) (pre-AIA) because it was published more than one year prior to August 25, 2006, the earliest effective filing date for the claims of the '438 patent. Gerber was submitted in a post-allowance IDS dated October 3, 2013. Gerber was therefore of record, but neither asserted by the Examiner nor argued by the Applicants, during prosecution of the '438 patent.

Gerber described ketoconazole as "a potent inhibitor of gonadal and adrenocortical steroid synthesis." MYL Ex. 1004 at 1177. Gerber also described the known cytotoxic effects of ketoconazole on prostate cancer cells and suggested ketoconazole's potential role in the treatment of prostate cancer. MYL Ex. 1004 at 1177.

Gerber taught the use of ketoconazole, a known CYP17 enzyme inhibitor and a potent inhibitor of gonadal and adrenocortical steroid synthesis, with prednisone in patients with hormone refractory metastatic prostate cancer. MYL Ex. 1004 at Abstract. In particular, Gerber taught that patients having progressive

prostate cancer despite androgen ablation, and therefore unresponsive to initial hormonal therapy, may benefit from the combination of ketoconazole and prednisone. MYL Ex. 1004 at Abstract, 1179.

The Gerber study combined daily administration of 600–900 mg ketoconazole with the administration of 5 mg prednisone twice daily. MYL Ex. 1004 at 1177-78. Gerber showed that 80% (12 out of 15) of patients with prostate cancer characterized by progressively increasing prostate specific antigen ("PSA") levels experienced a decrease in PSA levels in response to treatment with ketoconazole and prednisone. MYL Ex. 1004 at 1178–79. Gerber also showed that 75% of the patients who had bone pain and/or other symptoms of advancing malignancy at the outset of the study had subjective improvement. MYL Ex. 1004 at 1178–79. Gerber further reported that 20% (3 out of 15) of patients experienced a prolonged (8- to 10-month) favorable response to ketoconazole and prednisone based on persistently decreasing PSA levels and symptomatic improvement, including improvement in bone pain. MYL Ex. 1004 at 1178–79. Gerber further reported that this response rate was similar to that found in studies assessing response by monitoring changes in measurable tumor size, bone scan abnormalities and acid phosphatase. MYL Ex. 1004 at 1179. Gerber concluded that some patients with progressive prostate cancer despite previous hormone therapy will

derive significant benefit from the combination of ketoconazole and glucocorticoid replacement therapy. MYL Ex. 1004 at 1179.

c. In 1997, the '213 Patent Disclosed Abiraterone Acetate and Its Superiority over Ketoconazole in Treating Prostate Cancer

U.S. Patent 5,604,213 ("the '213 patent," MYL Ex. 1005), entitled "17-Substituted Steroids Useful in Cancer Treatment," issued to Barrie *et al.* on February 18, 1997. The '213 patent is prior art to the '438 patent under at least 35 U.S.C. § 102(b) (pre-AIA) because it issued more than one year prior to August 25, 2006, the earliest effective filing date for the claims of the '438 patent.

The '213 patent is listed in the FDA's Orange Book for Zytiga. The '213 patent is not related to the '438 Patent and there is no overlap in inventorship between the '213 patent and the '438 Patent. The '213 patent is assigned on its face to British Technology Group, Ltd. Of note, the '213 patent is incorporated by reference in the '438 patent, but the '213 patent was neither argued nor disclosed to the PTO in an IDS during prosecution of the '438 patent.

The '213 patent relates to a novel class of 17-substituted steroids and their use in the treatment of androgen-dependent and estrogen-dependent disorders, especially prostatic cancer and breast cancer, respectively. MYL Ex. 1005 at col. 1, ll. 11–14. The compounds disclosed and claimed in the '213 patent include abiraterone generally, and its acid addition salts and 3-esters (*see, e.g.*, MYL Ex.

1005 at col. 5, ll. 21–26; Example 2 at col. 11, ll. 36–55), as well as abiraterone acetate in particular (*see, e.g.*, MYL Ex. 1005 at col. 10, l. 62 – col. 11, l. 35 (Example 1)).

The ’213 patent further disclosed that abiraterone acetate may be administered in a method of treating androgen- and estrogen-dependent disorders, especially prostate cancer, as a pharmaceutical composition comprising a therapeutically effective amount of the compound, which the ’213 patent further disclosed to be 20–800 mg of abiraterone acetate per patient, per day. MYL Ex. 1005 at col. 10, ll. 27–57.

The ’213 patent disclosed that the CYP17 enzyme complex is known to be essential for the biosynthesis of androgens and estrogens. MYL Ex. 1005 at col. 1, ll. 17–19. The ’213 patent further disclosed that in the treatment of androgen-dependent disorders, especially prostatic cancer, there is a need for strong CYP17 inhibitors. MYL Ex. 1005 at col. 1, ll. 19–22.

The ’213 patent reported results from *in vitro* inhibition assays using tissue from the testes of previously untreated human patients undergoing orchiectomy for prostatic cancer. The assays compared the *in vitro* inhibition of 17α-hydroxyprogesterone, androstenedione, and testosterone production by some of the compounds of the invention, including abiraterone acetate (*i.e.*, Example 1) with that of ketoconazole. MYL Ex. 1005 at col. 21, l. 26–25, l. 12. The ’213 patent

reported the IC50 for abiraterone acetate as 0.0097 against lyase and 0.0130 against hydroxylase. MYL Ex. 1005 at col. 22, ll. 58–66. By comparison, the '213 patent reported the IC50 for ketoconazole as 0.026 against lyase (*i.e.*, an order of magnitude higher than abiraterone acetate) and 0.065 against hydroxylase. MYL Ex. 1005 at col. 24, ll. 61–62.

The '213 patent further disclosed the results of *in vivo* assays involving male human wild-type mice that compared the effect on organ weight and production of testosterone and luteinizing hormone of administering abiraterone acetate and ketoconazole, respectively. MYL Ex. 1005 at col. 25, l. 13 – col. 26, l. 63. The mice were tested for the presence of testosterone and luteinizing hormone. Post-mortem analyses of the adrenals, prostate, seminal vesicles, testes and kidneys were also conducted. MYL Ex. 1005 at col. 25, ll. 14–40. The results show that the reductions in weight of all of the prostate, seminal vesicles, testes and kidneys were much greater for the test compounds of the invention than for ketoconazole. MYL Ex. 1005 at col. 25, l. 50–26, l. 26; Table 3.

The '213 patent concluded that abiraterone acetate inhibits androgen, and particularly testosterone, synthesis in mammalian assays. MYL Ex. 1005 at col. 26, ll. 27–63; Table 4. The '213 patent further concluded that administering abiraterone acetate yielded a markedly greater decrease in testosterone levels than did administering ketoconazole. MYL Ex. 1005 at col. 26, ll. 32–38.

F. Explanation of Grounds for Unpatentability

1. The Method of Claim 1 was Obvious over Either O'Donnell in view of Gerber (Ground 1) or the '213 Patent in View of Gerber (Ground 2)

a. O'Donnell and the '213 Patent Disclosed the Use of Abiraterone Acetate to Treat Prostate Cancer

Claim 1 is obvious over O'Donnell in view of Gerber (Ground 1) or the '213 Patent in view of Gerber (Ground 2). MYL Ex. 1002, Garnick Decl. ¶¶54–59. Claim 1 is the only independent claim in the '438 patent. Claim 1 is directed to a method for treating prostate cancer in a human comprising administering therapeutically effective amounts of abiraterone acetate, or a pharmaceutically acceptable salt thereof, and prednisone. Because the prior art disclosed both the use of abiraterone acetate to treat prostate cancer, and co-administering prednisone in treatment of prostate cancer with a CYP17 inhibitor, with sufficient motivation to combine, claim 1 was obvious.

Regarding the use of abiraterone acetate, both O'Donnell and the '213 patent taught that abiraterone acetate is a selective CYP17 inhibitor that is more effective than ketoconazole, a CYP17 inhibitor known in the art, in suppressing testosterone levels in a mammal *in vivo*. MYL Ex. 1003, O'Donnell, at 2318, 2322, 2323, 2325; MYL Ex. 1005, the '213 patent, col. 25, l. 13 – col. 26, l. 63. O'Donnell taught that 500–800 mg of abiraterone acetate can be useful in suppressing testosterone levels in a human patient with prostate cancer, including metastatic

refractory prostate cancer. MYL Ex. 1003, O'Donnell, Abstract. The '213 patent disclosed that abiraterone acetate may be administered in a method of treating androgen- and estrogen-dependent disorders, especially prostate cancer, as a pharmaceutical composition. MYL Ex. 1005, the '213 patent, col. 10, ll. 47–56. The '213 patent further disclosed that a therapeutically effective amount of abiraterone acetate comprises a dose of 20–800 mg per patient, per day. MYL Ex. 1005, the '213 patent, col. 10, ll. 55–56. The '213 patent also taught that an abiraterone acetate salt may be administered to a human patient with prostate cancer to treat prostate cancer in said human patient. MYL Ex. 1005, the '213 patent, col. 10, ll. 22–50.

It would therefore have been obvious in light of the teachings of either O'Donnell or the '213 patent to administer a therapeutically effective amount of abiraterone acetate to a human patient with prostate cancer, to treat the patient's prostate cancer.

b. Gerber Disclosed Co-Administering Prednisone with a CYP17 Inhibitor, like Abiraterone Acetate

O'Donnell taught that concomitant hormone replacement therapy with a glucocorticoid may be needed when using abiraterone acetate to treat a prostate cancer in a human patient. *See, e.g.*, MYL Ex. 1003, O'Donnell, Abstract, 2323. Gerber taught that the combination of ketoconazole and prednisone (a glucocorticoid) is safe and effective in treating human patients with hormone-

refractory advanced prostate cancer. Exhibit 1005, Gerber, Abstract, 1177–1178, 1179. One of skill in the art would have been motivated to add prednisone to a method of using abiraterone acetate (a CYP17 inhibitor) to treat prostate cancer in a human patient by Gerber's teaching that administering 5 mg prednisone twice daily with ketoconazole, also a CYP17 inhibitor, is a safe and effective treatment in human patients with hormone-refractory prostate cancer. MYL Ex. 1004, Gerber, Abstract 1177–1178, 1179. One of skill in the art could also have been motivated by suggestions in the prior art that prednisone could have some amount of anti-cancer activity. MYL Ex. 1002, Garnick Decl. ¶¶ 33, 89–90.

As such, the skilled artisan would have expected that adding 10 mg of prednisone daily, according to Gerber, to the treatment regimen of O'Donnell, also would be safe and effective in treating a prostate cancer, including prostate cancer refractory to anticancer therapy, including hormone and anti-androgen therapy.

Alternatively, the '213 patent taught that abiraterone acetate is a CYP17 inhibitor that is more effective than ketoconazole, a CYP17 inhibitor known in the art, in suppressing testosterone levels in a mammal *in vivo*. MYL Ex. 1005, the '213 patent, col. 25, l. 13 – col. 26, l. 63. Gerber taught that combining ketoconazole with prednisone was safe and effective in treating human patients with hormone-refractory prostate cancer. MYL Ex. 1004, Gerber, Abstract, 1177–1178, 1179. The motivation to add prednisone to the method of treating prostate

cancer of the ’213 patent is clearly seen in Gerber who teaches that the administration of ketoconazole, a CYP17 inhibitor, in combination with 5 mg prednisone twice daily, is safe and effective in treating human patients with hormone-refractory prostate cancer. MYL Ex. 1004, Gerber, Abstract 1177– 1178, 1179. As such, the skilled artisan would expect that adding 5 mg twice daily prednisone to the treatment regimen of the ’213 patent would also be safe and effective in treating a prostate cancer in such patients, including prostate cancer refractory to anti-cancer therapy, including hormone and anti-androgen therapy.

Therefore, based on the teaching of either O’Donnell in view of Gerber or the ’213 patent in view of Gerber, one of skill in the art would have been motivated to co-administer 10 mg of prednisone daily with abiraterone acetate, a more selective CYP17 inhibitor than ketoconazole, to treat a human patient with prostate cancer, including prostate cancer refractory to previous anti-cancer therapy, including hormone and anti-androgen therapy, with a reasonable expectation that such treatment would be successful. One of skill in the art could also have been motivated by suggestions in the prior art that prednisone could have some amount of anti-cancer activity, with a similar expectation. MYL Ex. 1002, Garnick Decl. ¶¶ 33, 89–90.

Claims 2–20 all depend directly or indirectly from claim 1, and include additional limitations combining one or more of the following: i) the amount

and/or dosage range of abiraterone acetate or a pharmaceutically acceptable salt thereof to be administered; ii) the amount and/or dosage range of prednisone to be administered; iii) the type of prostate cancer to be treated; and iv) whether the patient has been previously treated with another anti-cancer agent, where the additional anti-cancer agent may be a hormonal ablation agent, an anti-androgen agent, or an anti-neoplastic agent. MYL Ex. 1002, Garnick Decl. ¶60. For the reasons set forth above regarding claim 1, and additionally for the reasons set forth below, these additional limitations also were obvious over O'Donnell in view of Gerber and/or the '213 patent in view of Gerber. MYL Ex. 1002, Garnick Decl. ¶¶60–76.

2. O'Donnell and the '213 Disclosed the Dosing Limitations Recited in Claims 2 and 3

O'Donnell taught that 500–800 mg of abiraterone acetate can be useful in suppressing testosterone levels in a human patient with prostate cancer, including advanced prostate cancer. *See, e.g.*, MYL Ex. 1003, O'Donnell, Abstract, 2318. The '213 patent taught that a therapeutically effective amount of abiraterone acetate for treating prostate cancer in a human patient includes 20–800 mg/day. MYL Ex. 1005, the '213 patent, col. 10, ll. 47–56.

A therapeutically effective amount of 500–800 mg of abiraterone acetate, as taught by O'Donnell, or 20–800 mg per day of abiraterone acetate, as taught by the '213 patent, is within the claimed ranges of "about 50 mg/day to about 2000

mg/day" (claim 2) and "about 500 mg/day to about 1500 mg/day" (claim 3). *See* MYL Ex. 1001, claims 2 & 3; MYL Ex. 1003, O'Donnell, Abstract; MYL Ex. 1005, the '213 patent, col. 10, ll. 47-56. Therefore, the daily dosage amounts and ranges of abiraterone acetate recited in these claims were disclosed in both O'Donnell and the '213 patent. MYL Ex. 1002, Garnick Decl. ¶¶61–62.

Therefore claims 2 and 3 were obvious over O'Donnell in view of Gerber (Ground 1) or the '213 patent in view of Gerber (Ground 2). MYL Ex. 1002, Garnick Decl. ¶¶61–62.

3. The Dose Recited in Claim 4 was Disclosed to One of Skill in the Art by either O'Donnell or the '213 Patent

O'Donnell disclosed a dose of 500–800 mg/day of abiraterone acetate used in Phase 1 human studies. MYL Ex. 1003, Abstract, 2319. The' 213 patent disclosed using 20–800 mg/day of abiraterone acetate. MYL Ex. 1005, the '213 patent, col. 10, ll. 55–56. O'Donnell reported that a dose of 800 mg of abiraterone acetate "can successfully suppress testosterone levels to the castrate range[, but] this level of suppression may not be sustained in all patients due to compensatory hypersecretion of LH" (luteinizing hormone). MYL Ex. 1003, O'Donnell, Abstract. O'Donnell therefore concluded from the studies that in the face of increased LH, higher doses of abiraterone acetate may be required. *See, e.g.*, MYL Ex. 1003, O'Donnell, Abstract; 2324.

It would have been obvious to one of skill in the art to optimize, to 1000 mg/day, the dose of abiraterone acetate administered to treat prostate cancer in a human patient, based on O'Donnell's teaching that adjustments in the dosage amount of abiraterone acetate may be necessary to treat a patient. In addition, with respect to both O'Donnell and the '213 patent, optimizing the dosage range and dosage regimen when administering active ingredients was well within the abilities of an ordinary skilled artisan in the pharmaceutical sciences as of at least 2006.

Thus, based on the teachings of O'Donnell or the '213 patent, it would have been well within the skill of one in the art to optimize the amount of abiraterone acetate to be administered to treat prostate cancer in a human patient, and obvious to do so. MYL Ex. 1002, Garnick Decl. ¶¶61–64.

4. The Dose Recited in Claim 5 was Disclosed to One of Skill in the Art by O'Donnell

O'Donnell teaches that capsules containing 10, 50, 100, and 200 mg of abiraterone acetate were provided for three Phase 1 clinical studies. MYL Ex. 1003, O'Donnell, 2319. It would have required only routine experimentation to increase the amount of abiraterone acetate in the capsules from 200 mg to 250 mg. *Id.*; *see also* MYL Ex. 1002, Garnick Decl. ¶65. Motivation for making this increase includes the starting dose of 500 mg in Study C and the use of 500 mg of abiraterone in Studies A and B, each of which is a multiple of 250 mg. MYL Ex. 1003, O'Donnell, 2319; *see also* MYL Ex. 1002, Garnick Decl. ¶65. Therefore,

one of skill in the art would have made a 250-mg dosage form of abiraterone acetate for the convenience of dosing. MYL Ex. 1002, Garnick Decl. ¶65. For at least this reason, claim 5 is obvious over O'Donnell in view of Gerber.

5. Claims 6–9 were Obvious over O'Donnell or the '213 Patent in View of Gerber

Claims 6–9 are directed to the amount or range of amounts of prednisone administered to a patient: "about 0.01 mg/day to about 500 mg/day" (claim 6); "about 10 mg/day to about 250 mg/day" (claim 7); "about 10 mg/day" (claim 8); and "one dosage form comprising about 5 mg of prednisone" (claim 9). MYL Ex. 1001. Gerber disclosed each of these limitations when it taught that the combination of ketoconazole, a CYP17 inhibitor, and 5 mg of prednisone twice daily is safe and effective in treating patients with hormone-refractory advanced prostate cancer. MYL Ex. 1004, Gerber. MYL Ex. 1002, Garnick Decl. ¶¶66–70.

Claim 6 depends from claim 1 and was therefore obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 was obvious and further for the disclosure in Gerber of 10 mg/day of prednisone. MYL Ex. 1002, Garnick Decl. ¶¶66–70.

Claim 7 depends from claim 6 and narrows the claimed range to about 10 mg/day to about 250 mg/day of prednisone. Because Gerber disclosed 10 mg/day of prednisone, claim 7 was obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 was obvious and further

for the disclosure in Gerber of 10 mg/day of prednisone. MYL Ex. 1002, Garnick Decl. ¶¶66–70.

Claim 8 depends from claim 7 and narrows the range to about 10 mg/day of prednisone. Because Gerber disclosed 10 mg/day of prednisone, claim 8 was obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 was obvious and further for the disclosure in Gerber of 10 mg/day of prednisone. MYL Ex. 1002, Garnick Decl. ¶¶66–70.

Claim 9 depends from claim 1 and requires the dosage form to include about 5 mg of prednisone. Because Gerber disclosed administering 5 mg of prednisone twice daily, a dosage form of 5 mg of prednisone would have been obvious. As such, claim 9 was obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 was obvious and further for the disclosure in Gerber of administering 5 mg of prednisone. MYL Ex. 1002, Garnick Decl. ¶¶66–70.

6. Claim 10 was Obvious over O'Donnell or the '213 Patent in View of Gerber

Claim 10 depends from claim 1 and recites the limitations of about 500 mg/day to about 1500 mg/day of abiraterone acetate and about 0.01 mg/day to about 500 mg/day of prednisone. MYL Ex. 1001. These limitations are also recited in claims 3 and 6, respectively. Therefore claim 10 was invalid as being obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for

the reasons set out above for claims 1, 3 and 6. MYL Ex. 1002, Garnick Decl. ¶¶66–70.

7. Claim 11 was Obvious over O'Donnell or the '213 Patent in View of Gerber

Claim 11 depends from claim 10 and recites the limitations of about 1000 mg/day of abiraterone acetate and about 10 mg/day of prednisone. MYL Ex. 1001. These limitations are also recited in claims 4 and 8, respectively. Claim 11 was therefore invalid as being obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the reasons set out above for claims 1, 4, 8, and 10. MYL Ex. 1002, Garnick Decl. ¶¶61–64.

8. Claims 12–16 were Obvious over O'Donnell in View of Gerber

Claim 12 depends from claim 1 and includes the limitations of the prostate cancer being refractory prostate cancer. Claim 13 depends from claim 12 and requires the refractory prostate cancer to be not responding to at least one anti-cancer agent. Claim 14 depends from claim 13 and required the anti-cancer agent to be a hormonal ablation agent, an anti-androgen agent or an anti-neoplastic agent. Claim 15 depends from claim 14 and requires the hormonal ablation agent to be deslorelin, leuprolide, goserelin, or triptorelin. Claim 16 depends from claim 14 and requires the anti-androgen agent to be bicalutamide, flutamide, or nilutamide.

The patients in the Phase I trial reported in O'Donnell were classified as having advanced or metastatic refractory prostate cancer. MYL Ex. 1003, O'Donnell, Abstract, 2318–2319. In addition, one of the cohorts in O'Donnell had undergone hormone ablation surgery, *i.e.*, orchiectomy, and all three cohorts of patients in O'Donnell had previously undergone hormone or anti-androgen therapy or both, and therefore had been previously treated with at least one anti-cancer agent, and in particular a hormone ablation agent or anti-androgen agent. MYL Ex. 1003, O'Donnell, Abstract; 2318–2320. In Study A, all patients had received flutamide or cyproterone acetate, the former being an anti-androgen agent recited in claim 16, and were receiving goserelin or leuprorelin, hormone ablation agents. MYL Ex. 1003, O'Donnell, 2320. Therefore claims 12 and 13 were obvious for the reasons set forth for claim 1 and additionally because O'Donnell taught that abiraterone acetate may be administered to treat a human patient with metastatic prostate cancer that is refractory to at least one anti-cancer agent. MYL Ex. 1002, Garnick Decl. ¶¶71–72.

Claim 14 was obvious for the reasons set forth for claims 1, 12, and 13 and additionally because O'Donnell taught that all three cohorts of patients in O'Donnell previously underwent hormone or anti-androgen therapy, or both. MYL Ex. 1002, Garnick Decl. ¶73.

Claim 15 was obvious for the reasons set forth for claims 1, 12, 13, and 14 and additionally because O'Donnell taught that the patients in Study A previously underwent hormone ablation therapy with goserelin or leuprorelin. MYL Ex. 1002, Garnick Decl. ¶73.

Claim 16 was obvious for the reasons set forth for claims 1, 12, 13, and 14 and additionally because O'Donnell taught that the patients in Study A previously underwent anti-androgen therapy with flutamide. MYL Ex. 1002, Garnick Decl. ¶73.

9. The Docetaxel Treatment in Claim 17 was Part of the Background Knowledge of One of Skill in the Art

Claim 17 depends from claim 14 and includes the limitations that the anti-neoplastic agent is docetaxel.

Docetaxel was well known as an anti-cancer compound, and, in particular, an anti-neoplastic agent at the priority date of the '438 Patent. For instance, U.S. Patent No. 5,688,977 (MYL Ex. 1029) which issued on November 18, 1997, disclosed that docetaxel is an anti-cancer compound. *See id.* at col. 2, ll. 29–32. And docetaxel in combination with prednisone was known to increase overall survival of patients with metastatic refractory prostate cancer, (MYL Ex. 1022, Tannock, Abstract), the first treatment known to do so, and was approved for the treatment of metastatic refractory prostate in 2004. *See,* MYL Ex. 1030, FDA News Release dated May 19, 2004. Therefore, claim 17 was obvious over

O'Donnell in view of Gerber for the reasons set forth for claim 14 and additionally because the background knowledge in the art taught that docetaxel with prednisone was a first-line treatment for metastatic hormone-refractory prostate cancer, known to increase overall survival. MYL Ex. 1002, Garnick Decl. ¶74.

10. Claim 18 was Obvious over O'Donnell in View of Gerber

Claim 18 depends from claim 12 and includes the limitations from claim 10 of about 500 mg/day to about 1500 mg/day of abiraterone acetate and about 0.01 mg/day to about 500 mg/day of prednisone. MYL Ex. 1001. Claim 18 was therefore invalid as obvious over O'Donnell in view of Gerber for the reasons set out above for claims 10 and 12. MYL Ex. 1002, Garnick Decl. ¶¶66–70, 75.

11. Claim 19 was Obvious over O'Donnell in View of Gerber

Claim 19 depends from claim 18 and includes the limitations from claim 11 of about 1000 mg/day of abiraterone acetate and about 10 mg/day of prednisone. MYL Ex. 1001. Claim 19 was therefore invalid as obvious over O'Donnell in view of Gerber for the reasons set out above for claims 11 and 18. MYL Ex. 1002, Garnick Decl. ¶76.

12. Claim 20 was Obvious over O'Donnell in View of Gerber

Claim 20 depends from claim 17 and includes the limitations from claim 11 of about 1000 mg/day of abiraterone acetate and about 10 mg/day of prednisone. Claim 20 was therefore invalid as obvious over O'Donnell in view of Gerber for the reasons set out above for claims 11 and 17. MYL Ex. 1002, Garnick Decl. ¶76.

G. Secondary Considerations do not Indicate that the Claims of the '438 Patent were Non-Obvious

To counter the *prima facie* evidence that all claims of the '438 patent are obvious, the patent owner may try to rely on secondary considerations of non-obviousness. While any such evidence would be "insufficient" to "overcome the strong showing of obviousness" here, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007), petitioner nonetheless preliminarily addresses certain alleged secondary considerations below, and reserves the right to respond to any arguments by the patent owner asserted in this proceeding.

1. Applicants did not Offer Relevant Evidence of Commercial Success and the Examiner Issued the '438 Patent Based on the Erroneous Conclusion that the Asserted Commercial Success of Zytiga Overcame the Obviousness of the Claimed Invention.

Applicants asserted during prosecution that the commercial success of Zytiga, a commercial product containing abiraterone acetate, was evidence of the non-obviousness of the claimed invention. MYL Ex. 1012 at 8. The Examiner erroneously concluded that the alleged "unexpected commercial success of the launch of the drug", Zytiga, obviated the obviousness rejection over O'Donnell and Tannock. MYL Ex. 1013; MYL Ex. 1014; MYL Ex. 1015; MYL Ex. 1017, Hofmann Decl. ¶20. This was error.

It is well settled that evidence of secondary considerations, such as commercial success, is only relevant to an obviousness analysis if the patentee can

show a direct link, or nexus, between the alleged secondary consideration and the claims of the patent. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 305 n.42 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). In addition, the proffered evidence must be commensurate in scope with the asserted claims. *Id.* Commercial success must be derived from the claimed invention. *Smith & Nephew, Inc. v. ConvaTec Techs., Inc.*, Case Nos. IPR2013-00097 and IPR2013-00102 (PTAB May 29, 2014); MPEP § 716.03(b).

An applicant asserting commercial success to overcome an obviousness rejection bears the burden of proof of establishing a nexus between the claimed invention and evidence of commercial success. MPEP § 716.03.

During prosecution, Applicants alleged that Zytiga's market shares of 70% in the "post-chemo" mCRPC market prior to the launch of Xtandi and 57% after the launch of Xtandi indicated that the claimed invention was a commercial success. MYL Ex. 1012 at 7-8, slide 12. But this information was misleading and incomplete, and could not suffice as a basis for allowing the '438 patent because Zytiga was not an unexpected commercial success when viewed in the proper market context. MYL Ex. 1017, Hofmann Decl. ¶¶ 35–38. Further, even assuming that the market definition Applicants used is accurate (and it is not), or that Applicants put Zytiga in the proper market context (which they did not), this information is insufficient as a matter of law because it fails to show any nexus

between the claimed combination and the commercial performance of Zytiga. MYL Ex. 1017, Hofmann Decl. ¶¶29–34.

Even assuming that Zytiga's commercial performance has been strong, regardless of how broadly the relevant therapeutic market is defined, any commercial success of Zytiga® has not been shown to derive from the claimed invention, *i.e.*, the combination of abiraterone acetate and prednisone. MYL Ex. 1017, Hofmann Decl. ¶¶29–35. Certainly, Applicants made no effort during prosecution of the '438 patent to show any nexus between the claimed invention and the commercial success of Zytiga®. Instead, any commercial success of Zytiga® is likely due to the effectiveness of abiraterone acetate, in isolation, in treating prostate cancer.

In particular, Applicants presented no evidence to suggest that the claimed invention, rather than the prior art abiraterone acetate, was responsible for any commercial success of Zytiga.® Instead, Applicants misled the Examiner by arguing that because Zytiga® is approved in combination with prednisone, Zytiga® is a commercial embodiment of the claimed invention. MYL Ex. 1012 at 7. Applicants then extrapolated that the sales of Zytiga® were evidence of the commercial success of the invention. However, this is incorrect as a matter of law because Zytiga® is the trade name under which abiraterone acetate is marketed.

And abiraterone acetate by itself is not a commercial embodiment of the claimed invention. Specifically, the active ingredient in Zytiga® is abiraterone acetate.

Abiraterone acetate and its use in treating prostate cancer are claimed in the '213 patent. Therefore, Zytiga® is a commercial embodiment of the '213 patent, not the '438 patent. In order to overcome the Examiner's *prima facie* case of obviousness by arguing commercial success, Applicants were required to provide sufficient evidence of a nexus between the commercial performance of Zytiga® and any incremental clinically significant anti-cancer benefit of administering the combination of abiraterone acetate and prednisone over abiraterone alone.

Applicants provided no such evidence. Having failed to do so, Applicants failed to meet their burden of proof.

2. One of Skill in the Art would not Anticipate Unexpected Benefits from the Claimed Invention and Applicants did not Offer Any Evidence of Relevant Unexpected Results

Although Zytiga® is approved in combination with prednisone, as Dr. Garnick explains, the anti-cancer effect of administering Zytiga® to treat prostate cancer is obtained from abiraterone acetate. MYL Ex. 1002, Garnick Decl. ¶93. This is because the prednisone administered with abiraterone in accordance with the approved indication for Zytiga® is intended as hormone replacement therapy related to administration of a CYP17 inhibitor, and not as an anti-cancer therapy. MYL Ex. 1002, Garnick Decl. ¶¶78–80, 84–88. Therefore, one of skill would not

expect the administration of the combination of abiraterone acetate and prednisone to provide any additional clinically significant anti-cancer benefit in treating prostate cancer beyond the anti-cancer benefit obtained from the administration of abiraterone acetate alone. MYL Ex. 1002, Garnick Decl. ¶¶84, 90.

Importantly, abiraterone acetate was known as an anti-cancer agent at least as of the earliest priority date of the claimed invention. In particular, abiraterone acetate was known as an anti-cancer agent for the treatment of prostate cancer. MYL Ex. 1002, Garnick Decl. ¶¶46, 55. For example, abiraterone acetate for the treatment of prostate cancer was disclosed and claimed in the '213 patent. MYL Ex. 1002, Garnick Decl. ¶¶46, 55, 83. Abiraterone acetate had been shown to reduce testosterone levels in refractory metastatic prostate cancer patients in clinical trials. MYL Ex. 1002, Garnick Decl. ¶¶46, 55. Therefore, the proper comparison for overcoming obviousness over the prior art based on unexpected results should have been whether there was any unexpected synergistic anti-cancer benefit of using the combination of abiraterone and prednisone beyond the anti-cancer effect of abiraterone alone. MYL Ex. 1002, Garnick Decl. ¶¶ 81-83. However, there are no unexpected anti-cancer synergies arising from the co-administering abiraterone acetate and prednisone. MYL Ex. 1002 (Garnick Decl.) ¶¶ 91-93.

But Applicants never once argued unexpected results of administering abiraterone and prednisone over abiraterone alone. Instead, Applicants misled the Examiner by arguing alleged unexpected benefits of abiraterone and prednisone over prednisone and a placebo. *See, e.g.*, July 3, 2012 Response (MYL Ex. 1008), January 11, 2013 Response (MYL Ex. 1010); June 4, 2013 Response (MYL Ex. 1012). However, evidence of any purported benefits of abiraterone and prednisone over prednisone and a placebo is insufficient as a matter of law to overcome a *prima facie* case of obviousness over the closest prior art, *i.e.*, abiraterone disclosed in the '213 patent.

Tellingly, the assignee of the '438 patent and NDA holder, Janssen Biotech Inc., has never described the co-administration of prednisone with Zytiga® as enhancing the anti-cancer activity of Zytiga® in information provided to healthcare practitioners. MYL Ex. 1002, Garnick Decl. ¶¶85–88. Instead, in the prescribing information for Zytiga®, including the 2011 Approval Prescribing Information and the 2015 revised Prescribing Information and accompanying brochure on co-administration, it is explained that co-administration of prednisone with Zytiga® is intended to reduce adverse effects, such as hypertension, hypokalemia and fluid retention that may result from CYP17 inhibition of cortisol production and consequent ACTH drive. MYL Ex. 1018, 2011 Zytiga® Approval Prescribing

Information, at 3–6, 11; MYL Ex. 1019, 2015 Zytiga® Prescribing Information, Co-administration Brochure, at 2–3.

For example, the 2015 brochure "Putting Prednisone in Perspective," that accompanies the 2015 revised Prescribing Information for Zytiga®, states that "[p]rednisone reduces the incidence and severity of mineralocorticoid-related adverse reactions associated with Zytiga®" and that "[c]oadministration of prednisone [with Zytiga®] suppresses the ACTH drive and reduces the incidence and severity of mineralocorticoid excess adverse reactions." MYL Ex. 1019, 2015 Zytiga® Prescribing Information, Co-administration Brochure, at 2.

Indeed, the Zytiga® 2015 Prescribing Information makes clear that prednisone is co-administered as hormone replacement therapy and that "7.5 mg/day to 10 mg/day of prednisone is approximately the physiologic equivalent of the amount of endogenous cortisol normally produced on a daily basis." MYL Ex. 1019, 2015 Zytiga® Prescribing Information, Co-administration Brochure, at 3.

As Dr. Garnick explains in his accompanying declaration, it was known in the art that administering ketoconazole, a CYP17 inhibitor like abiraterone acetate, to treat a prostate cancer may result in significant side effects, such as hypertension, hypokalemia and fluid retention as a result of a decrease in cortisol levels and consequent ACTH drive. MYL Ex. 1002, Garnick Decl. ¶¶44, 78–80. These adverse effects reduced the safety of administering ketoconazole as a single

agent. MYL Ex. 1002, Garnick Decl. ¶¶44, 78–80. Therefore, it was common practice in the art to co-administer a glucocorticoid as replacement therapy when administering ketoconazole to treat prostate cancer in a human patient in order to improve the safety and enhance the tolerability of treatment. MYL Ex. 1002, Garnick Decl. ¶¶45, 78–80. The particular combination of ketoconazole and prednisone was known to be safe and effective in treating patients with metastatic refractory prostate cancer based on at least the teachings of Gerber. *See, e.g.*, Exhibit 1004, Gerber, Abstract; MYL Ex. 1002, Garnick Decl. ¶¶58–59, 78–80.

Based on at least these teachings, one of skill in the art would have had a reasonable expectation that administration of abiraterone, a CYP17 inhibitor like ketoconazole, to treat a patient with prostate cancer would require the co-administration of a glucocorticoid such as prednisone in order to improve safety and enhance tolerability of administration. MYL Ex. 1002, Garnick Decl. ¶¶58–59, 78–80.

To the extent that the co-administration of prednisone with abiraterone made treatment of prostate cancer with abiraterone safer and/or more tolerable, this greater safety and/or tolerability was expected, based on the teachings of the prior art, including Gerber and others. *See, e.g.*, MYL Ex. 1004, Gerber, Abstract, 1178–1179; MYL Ex. 1020, Harris, 544; MYL Ex. 1021, Oh, Abstract, 89-90;

MYL Ex. 1022, Tannock 2004, 1502; MYL Ex. 1003, O'Donnell, 2323; MYL Ex. 1002, Garnick Decl. ¶¶78–80, 84, 89-90.

3. The '438 Patent Satisfied No Long-Felt but Unmet Need

Patentees may argue that commercial performance of Zytiga® is evidence of long-felt but unmet need. However, as explained by Dr. Hofmann, any success of Zytiga® that is not a result of the alleged novel features of the claimed invention is irrelevant to secondary considerations. MYL Ex. 1017, Hofmann Decl. ¶¶23, 29-34. As Dr. Garnick explains, the combination of abiraterone acetate and prednisone does not produce unexpected results in anti-cancer benefit. MYL Ex. 1002, Garnick Decl. ¶¶84, 90, 93. In fact, the perception among clinicians is that the requirement to co-administer prednisone with Zytiga is a drawback to its use to treat prostate cancer, a drawback not shared by other, competitive, therapies. MYL Ex. 1002, Garnick Decl. ¶94-96. For at least these reasons, the combination of abiraterone and prednisone satisfied no long-felt need beyond what abiraterone may have done.

4. The '213 is a Blocking Patent that Limits the Applicability of Commercial Success

The Federal Circuit has held that the existence of a blocking patent limits the applicability of any evidence of commercial success to overcome a prima facie case of obviousness. *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376–77 (Fed. Cir. 2005) (where "market entry by others was precluded" as a

result of a patent covering the active ingredient and its method of use and FDA exclusivity, "the inference of non-obviousness of weekly-dosing, from evidence of commercial success, is weak."). Both abiraterone acetate and its use for the treatment of prostate cancer are claimed in the '213 patent. MYL Ex. 1002, Garnick Decl. ¶¶46, 55, 83. The FDA's Orange Book lists the '213 patent as covering Zytiga®.[4] Because the '213 patent claims abiraterone acetate and its use in a method of treating an androgen-dependent disorder, "no entity other than" the patentee "could have successfully brought [abiraterone acetate] to market." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740–41 (Fed. Cir. 2013). The ability of the patentees of the '213 to block additional research and development of abiraterone acetate limits the relevance of commercial success for the '438 patent. MYL Ex. 1017, Hofmann Decl. ¶¶22, 24–28.

As Dr. Hofmann explains, from an economic perspective, commercial success presumes that if an idea were obvious to market participants, then others would have brought that idea to market sooner had there been economic incentives to do so. MYL Ex. 1017, Hofmann Decl. ¶27. A finding of commercial success can, in some circumstances, support the notion that a patent was not obvious to

[4] MYL Ex. 1047, FDA Website, Orange Book, Zytiga (NDA 202379), http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202379&Product_No=001&table1=OB_Rx (accessed 6/30/2016)

those skilled in the art if those incentives for development existed. MYL Ex. 1017, Hofmann Decl. ¶21. However, in this case, the '213 patent was a blocking patent that limited economic incentives to develop the invention of the '438 patent. MYL Ex. 1017, Hofmann Decl. ¶¶25–26. As Dr. Hofmann explains, "the existence of the '213 Patent prevents the performance of Zytiga from providing objective evidence of nonobviousness of the '438 Patent." MYL Ex. 1017, Hofmann Decl. ¶28.

5. Copying by Generic Drug Makers is Irrelevant

Finally, the Patentees may argue that petitioner and other generic drug companies seek to copy the invention of the '438 Patent by commercializing generic versions of abiraterone acetate. Because copying "is required for FDA approval" of generic drugs, any "evidence of copying in the [generic drug] context is not probative of nonobviousness." *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

H. Conclusion

For the reasons discussed above, petitioner requests that the Board institute an *inter partes* review and determine that all claims (1–20) of the '438 patent be canceled as unpatentable.

Respectfully submitted,

Dated: June 30, 2016

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

This Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1) because this Petition contains 13,342 words, as determined by the word-count function of Microsoft Word, excluding the parts of the Petition exempted by Rule (i.e., a table of contents, a table of authorities, mandatory notices under 37 C.F.R. § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing).

Date: June 30, 2016

/s/ *Brandon M. White*
Brandon M. White

Counsel for Petitioner Mylan Pharmaceuticals Inc.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: Petition for *Inter Partes* Review of U.S. Patent No. 8,822,438 by Federal Express Next Business Day Delivery on this day on the Patent Owner's correspondence address of record for the subject patent as follows:

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Los Angeles, CA 90024

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and by email to the service addresses for Patent Owner listed in Paper No. 13 in IPR2016-00286:

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