

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC,

Petitioner

v.

JANSSEN ONCOLOGY, INC.,

Patent Owner

U.S. Patent No. 8,822,438 to Auerbach *et al.* Issue Date: September 2, 2014  
Title: Methods and Compositions for Treating Cancer

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*Inter Partes* Review No. IPR2016-01317

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**PETITION FOR *INTER PARTES* REVIEW**

*35 U.S.C. §§ 311-319*

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**LISTING OF EXHIBITS PURSUANT TO 37 C.F.R. § 42.63(e)**

<b>Exhibit</b>	<b>Description</b>
1001	U.S. Patent No. 8,822,438, Auerbach and Beldegrum, “Methods and Compositions for Treating Cancer” (“the ‘438 patent”)
1002	Declaration of Dr. Scott Serels, MD (“Serels Decl.”)
1003	O’Donnell, A. <i>et al.</i> , “Hormonal impact of the 17 $\alpha$ -hydroxylase/C <sub>17</sub> -20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer,” <i>British Journal of Cancer</i> , (90):2317-2325 (2004) (“O’Donnell”)
1004	Gerber, G.S. <i>et al.</i> , “Prostate specific antigen for assessing response to ketoconazole and prednisone in patients with hormone refractory metastatic cancer,” <i>The Journal of Urology</i> , 144(5):1177-9 (1990) (“Gerber”)
1005	U.S. Patent No. 5,604,213, Barrie S.E. <i>et al.</i> , “17-Substituted Steroids Useful In Cancer Treatment” (“the ‘213 patent”)
1006	Tannock <i>et al.</i> , “Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points,” <i>The Journal of Clinical Oncology</i> , 14:1756-1764 (1996) (“Tannock”)
1007	February 3, 2012 Office Action (excerpt from prosecution history of ‘438 patent)
1008	July 3, 2012 Response (excerpt from prosecution history of ‘438 patent)
1009	Ryan <i>et al.</i> , “Abiraterone in metastatic prostate cancer without previous chemotherapy,” <i>The New England Journal of Medicine</i> , 368:138-148 (2012).

1010	January 11, 2013 Response (excerpt from prosecution history of ‘438 patent)
1011	March 4, 2013 Office Action (excerpt from prosecution history of ‘438 patent)
1012	June 4, 2013 Response (excerpt from prosecution history of ‘438 patent)
1013	July 3, 2013 Notice of Allowance (excerpt from prosecution history of ‘438 patent)
1014	October 25, 2013 Notice of Allowance (excerpt from prosecution history of ‘438 patent)
1015	February 11, 2014 Notice of Allowance (excerpt from prosecution history of ‘438 patent)
1016	June 2, 2014 Notice of Allowance (excerpt from prosecution history of ‘438 patent)
1017	Declaration of Dr. DeForest McDuff, PhD (“McDuff Declaration”)
1018	2011 Zytiga® Approval Prescribing Information
1019	2015 Zytiga® Prescribing Information, Co-administration Brochure
1020	Harris <i>et al.</i> , “Low dose Ketoconazole with replacement doses of hydrocortisone in patients with progressive androgen independent prostate cancer,” <i>The Journal of Urology</i> , volume 168:542-545 (August 2002)
1021	William Oh, “Secondary hormonal therapies in the treatment of prostate cancer,” <i>Urology</i> , volume 60:87-93 (Supplement 3A) (September 2002)
1022	Tannock, I. <i>et al.</i> , “Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer,” <i>N. Eng. J. Med.</i> ,

	351:1502-12 (2004)
1023	Attard, G. <i>et al.</i> , “Selective blockade of androgenic steroid synthesis by novel lyase inhibitors as a therapeutic strategy for treating metastatic prostate cancer,” <i>Br. J. Urol.</i> 96(9): 1241-1246 (2005)
1024	Hellerstedt <i>et al.</i> , “The Current State of Hormonal Therapy for Prostate Cancer,” <i>CA Cancer J. Clin.</i> , 52:154-179 (2002).
1025	Kasper, D.L. <i>et al.</i> (Eds.), <i>Harrison's Principles of Internal Medicine</i> , 16 <sup>th</sup> Edition (2005), p. 549.
1026	Auchus, R.J. “The genetics, pathophysiology, and management of human deficiencies of P450c17,” <i>Endocrinol. Metab. Clin. North Am.</i> (30)1:101-119 (2001)
1027	Costa-Santos, M. <i>et al.</i> , “Two Prevalent CYP17 Mutations and Genotype-Phenotype Correlations in 24 Brazilian Patients with 17-Hydroxylase Deficiency,” <i>J. Clin. Endocrin. &amp; Metabol.</i> (89)1:49-
1028	Jubelirer, S.J., <i>et al.</i> , “High dose ketoconazole for the treatment of hormone refractory metastatic prostate carcinoma,” <i>J. Urol.</i> , 142(1):89-901 (1989)
1029	U.S. Patent 5,688,977, Sisti, N.J. <i>et al.</i> , “Method for Docetaxel Synthesis”
1030	U.S. Food and Drug Administration ("FDA") FDA News Release dated May 19, 2004, “FDA Approves New Indication for Taxotere-Prostate Cancer”
1031	Tannock, I. <i>et al.</i> , “Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response,” <i>Journal of Clin. Oncology</i> , 7:590-7 (1989)
1032	Taxotere® Prescribing Information (2004)
1033	Scher, H.I. <i>et al.</i> , “Increased survival with Enzalutamide in Prostate

	Cancer after Chemotherapy,” <i>New Eng. J. Med.</i> , 367:1187-97 (2012)
1034	de Bono, J.S. <i>et al.</i> , “Abiraterone and Increased Survival in Metastatic Prostate Cancer,” <i>New Engl. J. Med.</i> , 364:1995-2005 (2011)
1035	Orange Book listing for Zytiga®
1036	Initial Application (excerpt from prosecution history of ‘438 patent)
1037	November 25, 2011 Office Action (excerpt from prosecution history of ‘438 patent)
1038	December 21, 2011 Response (excerpt from prosecution history of ‘438 patent)
1039	September 11, 2012 Office Action (excerpt from prosecution history of ‘438 patent)
1040	Cancer.net (ASCO Patient Website), Treatment of Metastatic Castration-Resistant Prostate Cancer, <a href="http://www.cancer.net/research-and-advocacy/asco-careand-treatment-recommendations-patients/treatment-metastatic-castrationresistant-prostate-cancer">http://www.cancer.net/research-and-advocacy/asco-careand-treatment-recommendations-patients/treatment-metastatic-castrationresistant-prostate-cancer</a> (accessed 7/24/2015).
1041	Cancer.org (ACS), “What are the key statistics about prostate cancer?” <a href="http://www.cancer.org/cancer/prostatecancer/detailed-guide/prostatecancerkeystatistics">http://www.cancer.org/cancer/prostatecancer/detailed-guide/prostatecancerkeystatistics</a> (accessed 8/20/2015).
1042	Cowen & Company, “Biotechnology Quarterly,” 7/2/2012.
1043	Cowen & Company, “Quick Take – Johnson & Johnson,”
1044	Credit Suisse, “Prostate Cancer – Implications of Zytiga’s Pre-Chemo Approval,” 12/11/2012.
1045	FDA News Release, “FDA expands Zytiga’s use for late-stage prostate cancer,” 12/10/2012,

	<a href="http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm331492.htm">http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm331492.htm</a> .
1046	FDA Website, Drugs@FDA – Zytiga, <a href="http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fusection=SearchDrugDetails">http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fusection=SearchDrugDetails</a> (accessed 7/23/2015).
1047	FDA Website, Orange Book, Zytiga (NDA 202379), <a href="http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202379&amp;Product_No=001&amp;table1=OB_Rx">http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202379&amp;Product_No=001&amp;table1=OB_Rx</a> (accessed 7/24/2015).
1048	Galderma Laboratories, L.P. et al. v. Tolmar, Inc., 737 F.3d 731, 740–41 (Fed. Cir. 2013).
1049	Jevtana Website, Dosing and Administration, <a href="http://www.jevtana.com/hcp/dosing/default.aspx">http://www.jevtana.com/hcp/dosing/default.aspx</a> (accessed 8/20/2015).
1050	Kirby, M., C. Hirst, and E.D. Crawford (2011), “Characterising the Castration-Resistant Prostate Cancer Population: A Systematic Review,” <i>International Journal of Clinical Practice</i> 65(11): 1180-1192.
1051	Mayo Clinic Website, Prostate cancer, <a href="http://www.mayoclinic.org/diseasesconditions/prostate-cancer/basics/definition/con-20029597?p=1">http://www.mayoclinic.org/diseasesconditions/prostate-cancer/basics/definition/con-20029597?p=1</a> (accessed 7/24/2015).
1052	Medivation Press Release, “U.S. FDA Approves New Indication for the Use of XTANDI® (Enzalutamide) Capsules for Patients With Metastatic Castration-Resistant Prostate Cancer,” 9/10/2014, <a href="http://investors.medivation.com/releasedetail.cfm?ReleaseID=870267">http://investors.medivation.com/releasedetail.cfm?ReleaseID=870267</a> .
1053	Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc., 395 F.3d 1364, 1376–77 (Fed. Cir. 2005).
1054	Murphy, William J., John L. Orcutt, and Paul C. Remus (2012),



	<i>Patent Valuation: Improving Decision Making through Analysis</i> , Hoboken, NJ: Wiley.
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1056	RBC Capital Markets (via Barron's Website), "Xtandi Beats Casodex, Set to Top Zytiga," 4/3/2015, <a href="http://online.barrons.com/articles/xtandi-beats-casodexset-to-top-zytiga-1428075331">http://online.barrons.com/articles/xtandi-beats-casodexset-to-top-zytiga-1428075331</a> (accessed 7/24/2015).
1057	Syntex (U.S.A.) LLC and Allergan v. Apotex, Inc. et al., 407 F.3d 1371, 1383 (Fed. Cir. 2005).
1058	UBS Investment Research, "Johnson & Johnson – Zytiga Label Extended," 12/10/2012.
1059	UBS Research, "Medivation – A Look at the Growth and Share in Prostate Cancer," 2/3/2014.
1060	Wedbush Securities, Inc., "Medivation: Zytiga Market Share Decline Accelerates From Last Quarter," 7/14/2015.
1061	Wells Fargo Securities, LLC., "Johnson & Johnson," 6/29/2015.
1062	William Blair, "Biotechnology – Zytiga Fourth-Quarter Sales Imply Xtandi Strength," 1/22/2013.
1063	William Blair, "Medivation, Inc. – Looking into Recent Weaknesses," 7/15/2015.
1064	Zytiga Brochure, Putting Prednisone in Perspective, 3/2015.
1065	Zytiga Label, 5/20/2015.
1066	Zytiga Website, How Zytiga® (abiraterone acetate) Works,

	<a href="https://www.zytiga.com/print/about-zytiga/how-zytiga-works">https://www.zytiga.com/print/about-zytiga/how-zytiga-works</a> (accessed 7/23/2015).
1067	IMS Health Data 2012-2015 for Zytiga®, Xtandi® and Jevtana®
1068	<i>Reserved</i>
1069	<i>Reserved</i>
1070	<i>Reserved</i>
1071	<i>Reserved</i>
1072	<i>Reserved</i>
1073	Declaration of Devalingam Mahalingam, M.D., Ph.D.
1074	Curriculum Vitae of Devalingam Mahalingam, M.D., Ph.D.

## TABLE OF ABBREVIATIONS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AR	Androgen receptor
CRPC	Castration-resistant prostate cancer
mCRPC	Metastatic Castration-resistant prostate cancer
CYP17	17 $\alpha$ -hydroxylase/C <sub>17,20</sub> -lyase
DHT	Dihydrotestosterone
HWT mice	Human wild type mice
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

## **CHALLENGED CLAIMS OF U.S. PATENT NO. 8,822,438**

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

2. The method of claim 1, wherein the therapeutically effective amount of abiraterone acetate or pharmaceutically acceptable salt thereof is from about 50 mg/day to about 2000 mg/day.

3. The method of claim 2, wherein the therapeutically effective amount of abiraterone acetate or pharmaceutically acceptable salt thereof is from about 500 mg/day to about 1500 mg/day.

4. The method of claim 3, wherein the therapeutically effective amount of abiraterone acetate or pharmaceutically acceptable salt thereof is about 1000 mg/day.

5. The method of claim 1, wherein the therapeutically effective amount of the abiraterone acetate or a pharmaceutically acceptable salt thereof is administered in at least one dosage form comprising about 250 mg of abiraterone acetate or a pharmaceutically acceptable salt thereof.

6. The method of claim 1, wherein therapeutically effective amount of prednisone is from about 0.01 mg/day to about 500 mg/day.

7. The method of claim 6, wherein therapeutically effective amount of prednisone is from about 10 mg/day to about 250 mg/day.

8. The method of claim 7, wherein therapeutically effective amount of prednisone is about 10 mg/day.

9. The method of claim 1, wherein the therapeutically effective amount of prednisone is administered in at least one dosage form comprising about 5 mg of prednisone.

10. The method of claim 1, comprising administering to said human about 500 mg/day to about 1500 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 0.01 mg/day to about 500 mg/day of prednisone.

11. The method of claim 10, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

12. The method of claim 1, wherein said prostate cancer is refractory prostate cancer.

13. The method of claim 2, wherein refractory prostate cancer is not responding to at least one anti-cancer agent.

14. The method of claim 13, wherein at least one anti-cancer agent comprises a hormonal ablation agent, an anti-androgen agent, or anti-neoplastic agent.

15. The method of claim 14, wherein the hormonal ablation agent comprises deslorelin, leuprolide, goserelin, or triptorelin.

16. The method of claim 14, wherein the anti-androgen agent comprises bicalutamide, flutamide, or nilutamide.

17. The method of claim 14, wherein the antineoplastic agent comprises docetaxel.

18. The method of claim 12, comprising administering to said human about 500 mg/day to about 1500 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 0.01 mg/day to about 500 mg/day of prednisone.

19. The method of claim 18, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

20. The method of claim 17, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

## **I. INTRODUCTION**

Argentum Pharmaceuticals LLC ("Petitioner") requests that the Board institute *inter partes* review of and cancel claims 1-20 of U.S. Patent No. 8,822,438 to Auerbach *et al.* ("the '438 patent") (Ex. 1001), which is assigned to Janssen Oncology, Inc. ("Janssen"). *Inter partes* review of claims 1-20 of the '438 patent was instituted in IPR2016-00286 on May 31, 2016, based on a petition filed by Amerigen Pharmaceuticals, Ltd ("Amerigen IPR"). Petitioner hereby files its own Petition on the same grounds as those instituted in the Amerigen IPR and concurrently seeks to join the instituted Amerigen IPR proceeding (IPR2016-00286). A motion for joinder with IPR2016-00286 is being filed concurrently with this Petition.

## **II. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))**

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

The real parties in interest for this Petition are: Argentum Pharmaceuticals LLC; Intelligent Pharma Research LLC; APS GP LLC; and APS GP Investors LLC.

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

To the best of Petitioner's knowledge, the following litigations or other related matters related to the '438 patent that would affect, or be affected by, a decision in this proceeding are pending:

*BTG International Limited et al. v. Glenmark Pharmaceuticals Inc., USA et*

*al.*, 2-16-cv-03743 (District of New Jersey), filed June 24, 2016;

*BTG International Limited et al. v. Amerigen Pharmaceuticals, Inc. et al.*, 2-16-cv-02449 (District of New Jersey), filed May 2, 2016;

*Amerigen Pharmaceuticals Limited v. Janssen Oncology, Inc.*, IPR2016-00286, filed December 4, 2015, instituted on May 31, 2016;

*Janssen Biotech, Inc. et al. v. Mylan Pharmaceuticals Inc. et al.*, 1-15-cv-00130 (Northern District of West Virginia), filed August 4, 2015;

*Janssen Biotech, Inc. et al. v. Amneal Pharmaceuticals LLC et al.*, 1-15-cv-00679 (District of Delaware), filed August 3, 2015;

*BTG International Limited et al. v. Actavis Laboratories FL, Inc. et al.*, 9-15-cv-81076-DMM (Southern District of Florida), filed August 3, 2015; and

*BTG International Limited et al. v. Actavis Laboratories FL, Inc., et al.*, 2-15-cv-05909-KM-JBC (District of New Jersey), filed July 31, 2015.

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

<b>Lead Counsel</b>	<b>Back-Up Counsel</b>
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Filed concurrently herewith is a Power of Attorney pursuant to 37 C.F.R. §



42.10(b).

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

Please direct all correspondence regarding this Petition to lead counsel at the above address. Petitioner consents to service by email at: TRea@Crowell.com and SLentz@crowell.com.

**E. Service on Patent Owner Under 37 C.F.R. § 42.106(a) and 42.105(a)**

This petition is being served by FedEx® on Johnson & Johnson, owners of the '438 Patent, at the address of record according to the USPTO PAIR database: Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003.

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

Petitioner hereby certifies that the patent for which review is sought is available for *inter partes* review, and that the petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the Grounds identified in the petition.

**IV. PAYMENT OF FEES (37 C.F.R. § 42.103)**

The Office is authorized to charge the required fee, and any fee deficiencies and credit overpayments to Deposit Acct. No. 05-1323, Customer ID No. 23911.

**V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR (37 C.F.R. § 42.22(a))**

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 in detail in Sections XI-XIII below.

**VI. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))**

Petitioner respectfully requests *inter partes* review and cancellation of claims 1-20 of the ‘438 Patent based on the grounds set forth in the table below:<sup>1</sup>

<b>Ground</b>	<b>Challenged Claims</b>	<b>Statutory Basis</b>	<b>References</b>
1	1-20	§ 103	O’Donnell in view of Gerber
2	1-4 and 6-11	§ 103	‘213 patent in view of Gerber

Sections XI-XIII below explain how the ‘438 patent claims are unpatentable on the grounds listed above. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966) (obviousness analysis evaluates the level of ordinary skill in the art; the scope and content of the prior art; whether any differences between the prior art and the claims would have been obvious to the skilled artisan; and secondary considerations).

In support of these grounds for unpatentability, Petitioner submits the expert declaration of Dr. Scott Serels, M.D., (Ex. 1002 (“Serels Declaration”)), as well as

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<sup>1</sup> The grounds listed herein are consistent with those on which the Board instituted IPR of the challenged claims. *Amerigen Pharmaceuticals Ltd. v. Janssen Oncology, Inc.*, IPR2016-00286, Institution Decision, Paper 14 at page 19.

the declaration of Dr. Devalingam Mahalingam (Ex. 1073 (“Mahalingam Declaration”)) to discuss the relevant field and art in general, and the factual and opinion bases underlying Petitioner’s Grounds 1 and 2 for the *Graham* factors other than commercial success.<sup>2</sup> Petitioner also submits the expert declaration of economics expert Dr. DeForest McDuff, PhD (Ex. 1017 (“McDuff Declaration”)) on the secondary considerations of the *Graham* factors.

Petitioner also relies on the other Exhibits set forth in the concurrently filed Listing of Exhibits.

## **VII. INTRODUCTION AND SUMMARY OF ARGUMENT**

The claims of the ‘438 patent are directed to treating prostate cancer by administering therapeutically effective amounts of abiraterone acetate, a 17  $\alpha$ -hydroxylase/C<sub>17,20</sub>-lyase inhibitor (“CYP17 inhibitor”), in combination with prednisone, a glucocorticoid. The prior art taught use of abiraterone acetate as an effective anti-cancer agent which suppresses testosterone synthesis in prostate

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<sup>2</sup> Petitioner is willing to work with Amerigen and rely solely on Dr. Serels’ declaration and testimony and will withdraw the expert declaration of Dr. Mahalingam upon agreement of Amerigen to jointly rely on Dr. Serels. However, in the event that an agreement is not reached, Petitioner is prepared to rely on the declaration and testimony of Dr. Mahalingam. This position is more explicitly explained in the concurrently filed Motion for Joinder.

cancer patients. Ex. 1002, Serels Decl. ¶¶ 26, 45, 56, 58, Ex. 1073; Mahalingam Decl. ¶¶ 26, 45, 56, 58. It was known that testosterone promoted prostate cancer proliferation and progress so that to treat prostate cancer, testosterone synthesis must be suppressed.

However, it was known that in using a CYP17 inhibitor to reduce testosterone synthesis, the CYP17 inhibitor also undesirably suppressed the production of cortisol, a glucocorticoid, which is necessary for other biochemical cycles in the body and its reduced production caused adverse effects, including hypertension, hypokalemia (decrease in circulating potassium levels), and fluid retention. To address the suppressed synthesis of cortisol, the prior art also 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. Ex. 1002, Serels Decl. ¶¶ 32, 34, 48, Ex. 1073; Mahalingam Decl. ¶¶ 32, 34, 48.

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. Ex. 1002, Serels Decl. ¶¶ 36, 45, Ex. 1073; Mahalingam Decl. ¶¶ 36, 45. The prior art also taught that the combination of ketoconazole and prednisone

was a safe and effective treatment for refractory metastatic prostate cancer. Ex. 1002, Serels Decl. ¶48, Ex. 1073; Mahalingam Decl. ¶ 48.

One of skill in the art would have combined abiraterone acetate and prednisone based on 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 because the prior art taught abiraterone acetate as a more effective CYP17 inhibitor than ketoconazole and the combination of ketoconazole and prednisone as safe and effective to treat patients with hormone refractory metastatic prostate cancer. Ex. 1002, Serels Decl. ¶¶45-49; Ex. 1073, Mahalingam Decl. ¶¶ 45-49.

There are no secondary considerations of commercial success that overcome obviousness. The claims of the application resulting 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 method of treating prostate cancer by administering abiraterone acetate and prednisone) and any commercial success of the drug Zytiga®.

## **VIII. 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. Ex. 1002, Serels Decl. ¶8; Ex. 1073, Mahalingam Decl. ¶ 8. A person of ordinary skill in the art would be a physician specializing in urology or oncology, or holding a Ph.D. in pharmacology, biochemistry or a related discipline. Ex. 1002, Serels Decl. ¶8; Ex. 1073, Mahalingam Decl. ¶ 8. Additional experience could substitute for the advanced degree. Ex. 1002, Serels Decl. ¶8; Ex. 1073, Mahalingam Decl. ¶ 8. 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. Ex. 1002, Serels Decl. ¶9; Ex. 1073, Mahalingam Decl. ¶ 9. For example, one of skill may consult with an enzymologist and/or molecular biologist and thus may rely on the opinions of such specialists in evaluating the claims. Ex. 1002, Serels Decl. ¶10; Ex. 1073, Mahalingam Decl. ¶ 10.

## **IX. U.S. PATENT NO. 8,822,438 AND ITS FILE HISTORY**

### **A. Specification of the '438 Patent**

The "Background" section 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. 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.” The specification states that another treatment option for prostate cancer, hormone therapy, is less invasive than surgery and has fewer side effects. 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. Ex. 1001, Col. 1, ll. 25-64.

The “Summary of the Invention” section describes various embodiments of the invention being directed to methods and compositions of treating a refractory cancer in a patient, involving administration of 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. Ex. 1001, Col. 2, l. 9 – col. 3, l. 20.

The “Definitions” section defines “17 $\alpha$ -hydroxylase/C<sub>17,20</sub>-lyase inhibitor” as an inhibitor of the enzyme “17 $\alpha$ -hydroxylase/C<sub>17,20</sub>-lyase” (an enzyme involved in testosterone synthesis). Ex. 1001, Col. 3, l. 66 – col. 4, l. 7. The terms “treat,”

“treating” and “treatment” are defined as including the “eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer.” Ex. 1001, Col. 3, ll. 46-50. The term “anti-cancer agent” is defined as referring to “any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits stops or reduces the proliferation of cancer cells.” Ex. 1001, 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.” Ex. 1001, Col. 4, ll. 23-27.

The “Detailed Description of the Invention” section refers to U.S. Patent No.5,604,213 (“Barrie *et al.*”, 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.” Ex. 1001, Col. 5, ll. 23-29. The specification provides a list of various CYP17 inhibitors including abiraterone (3 $\beta$ -ol-17-(3-pyridyl) androsta-5,16-diene). 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. Ex. 1001, Col. 10, ll. 15-19. A single unit solid oral dosage forms



may contain about 50 mg to about 300 mg of abiraterone acetate and 0.5 to 3 mg of a steroid, e.g., glucocorticoid, optionally with additional excipients. 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. 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. 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. Ex. 1001, Col. 15, ll. 52-66.

#### **B. 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. The application was filed as a continuation of

Application No. 11/844,440, filed on August 24, 2011, which claims priority to Provisional Application No. 60/921,506, filed on August 25, 2006.

In an Office Action dated November 25, 2011, the Examiner imposed a restriction requirement 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). 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. 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 37-56 were rejected for obviousness over O'Donnell (Ex. 1003) in view of Tannock (Ex. 1006). The Examiner characterized O'Donnell as disclosing the CYP17 inhibitor abiraterone acetate being used to suppress testosterone levels in prostate cancer patients. February 3, 2012 Office Action (Ex. 1007) at p. 2. Tannock was cited for teaching 10 mg prednisone "in combination with another anti-cancer drug [i.e., mitoxantrone] as effective in treating refractory hormonal- resistant prostate cancer." Ex. 1007 at p. 3.

In a Response dated July 3, 2012, Applicants argued that "nothing 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

(Ex. 1008) at p. 2. Applicants further argued that “even if one of ordinary skill would have been motivated to combine both modes of treatment, the claimed invention produces unexpected results.” Ex. 1008 at p. 2.

Applicants provided as evidence to support unexpected results the disclosure of 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. Applicants described Sartor as teaching that “abiraterone plus prednisone prolongs overall survival relative to prednisone alone.” Ex. 1008 at p. 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. 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. Ex. 1008 at p. 3.

In a Final Office Action dated September 11, 2012, the Examiner maintained the rejection of the claims over O’Donnell and Tannock. In a Request for Continued Examination (“RCE”) and Response dated January 11, 2013, Applicants once again argued unexpected results and provided another reference, Ryan *et al.*,

*New Eng. J. of Med.*, 368:138-148 (2012) (Ex. 1009), purporting to show unexpected results of the claimed invention over prednisone. For example, Applicants argued an “unexpected survival benefit of abiraterone with prednisone” over “prednisone alone.” January 11, 2013 Response (Ex. 1010) at 7.

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. The Examiner explained that “since abiraterone acetate provide a new mechanism of action in treating prostate cancer and prednisone is known to be useful for treating cancer, concomitant employment of both compounds into a single method useful for the same purpose, treating prostate cancer, would be considered *prima facie* obvious.” Office Action dated March 4, 2013 (Ex. 1011) at p. 3.

However, as explained in the Serels 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. Second, prednisone was not typically used for clinically treating cancer. As explained in the Serels and Mahalingam Declarations (Ex. 1002, ¶¶74, 79, 80; Ex. 1073, ¶¶ 74, 79, 80, 88-93), in the 1980s there was a belief that prednisone might be useful for treating prostate cancer. At the time of filing of the ‘438 patent, however, it was common practice

to co-administer a glucocorticoid such as prednisone with a CYP17 inhibitor *for glucocorticoid replacement*. Ex. 1002, Serels Decl. ¶¶34, 48, 68; Ex. 1073, Mahalingam Decl. ¶¶ 34, 48, 68.

In a Notice of Appeal and Response dated June 4, 2013, Applicants reiterated their argument of Tannock purportedly teaching away from the use of prednisone with abiraterone acetate because Tannock teaches that “there was no significant difference in overall survival between prednisone alone and prednisone plus the cancer agent mitoxantrone.” Response dated June 4, 2013 (Ex.1012) at p. 6. 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 the same cancer agent in combination with prednisone.” Ex. 1012 at p. 6.

Applicants also provided the FDA approval label for Zytiga™ and argued that “taking Zytiga in accordance with the approved label [*i.e.*, in combination with prednisone] represents a commercial embodiment of the presently claimed invention.” Ex. 1012 at p. 7. Applicants also submitted a news release from the FDA announcing that Zytiga was approved for the additional indication for use in prostate cancer patients prior to receiving chemotherapy as purporting to provide additional evidence of commercial success of the claimed combination. Ex. 1012 at p. 7.

Applicants once again argued commercial success, this time based on market

share data for Zytiga®, and a 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.” Ex. 1012 at p. 7, slide 11.

Applicants specifically pointed to a slide showing a 70% market share for Zytiga in July 2012 for “chemo refractory prostate cancer patients.” Applicants argued that the Duato presentation showed that despite another product, Xtandi®, being introduced in August 2012, as of April 2013, Zytiga was still the market leader with 57% market share in “chemo-refractory prostate cancer patients.” Ex. 1012 at p. 7, slide 12. 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 prostate cancer despite an earlier introduced therapy [*i.e.*, Jevtana®] and a later introduced therapy [*i.e.*, Xtandi®].” Ex. 1012 at p. 8. Applicants argued that “this commercial success [of Zytiga] demonstrates the non-obviousness of the presently claimed invention.” Ex. 1012 at p. 8.

In a Notice of Allowance 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).” Notice of Allowance dated July 3, 2013 at 2 (emphasis added) (Ex. 1013).

In an Information Disclosure Statement (“IDS”) dated October 3, 2013 submitted with an RCE, Applicants provided a number of non-patent literature documents, following which a second Notice of Allowance was issued on October 25, 2013. Among the references listed in the October 3, 2013 IDS was Gerber (Ex. 1004). A second Notice of Allowance issued dated October 25, 2013 wherein the Examiner stated in the Notice of Allowability that the reasons for allowance were “essentially the same” as in the previous notice. Ex. 1013, at p. 2.

A second IDS submitted with a second RCE and listing additional non-patent documents was filed by Applicants on January 10, 2014, following which a third Notice of Allowance was issued on February 11, 2014. The Examiner again stated in the Notice of Allowability that the reasons for allowance were “essentially the same as in the initial notice” and further stated that “the commercial success of the combination of prednisone and abiraterone to treat prostate cancer obviate the rejection under 35 U.S.C. 103(a).” Ex. 1015 at p. 2.

A third IDS, dated May 9, 2014, listed a number of additional references. A fourth IDS, dated May 30, 2014, 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. A

fourth Notice of Allowance was issued on June 2, 2014, reiterating the same grounds for allowance as the previous notice. Ex. 1016.

**X. 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. Because the Board considered and adopted claim constructions in the Amerigen IPR, Petitioner will not separately address claim construction in the instant Petition. Further, Petitioner notes that the Board adopted the following constructions in the Amerigen IPR:

<b>Claim Term(s)</b>	<b>Construction</b>
“treat,” “treating,” and “treatment”	include the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer
“anti-cancer agent”	any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits, stops or reduces the proliferation of cancer cells
“refractory cancer”	cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment
“therapeutically effective amount of prednisone”	an amount of prednisone effective for treating prostate cancer

IPR2016-00286, Institution Decision, Paper 14 at pages 5-7.

In any separate proceedings, or if the circumstances in this proceeding change such that the Board decides that additional claim terms should be expressly constructed, or the Patent Owner asserts any differing claim constructions,



Argentum reserves their right to either propose express constructions or to respond thereto in later briefing.

## **XI. SCOPE AND CONTENT OF THE PRIOR ART**

### **A. 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. However, the prior art taught use of abiraterone acetate as an effective anti-cancer agent which suppresses testosterone synthesis in prostate cancer patients. Ex. 1002, Serels Decl. at ¶¶26, 27, 36, 45; Ex. 1073, Mahalingam Decl. ¶¶ 26, 27, 36, 45. The prior art also 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. Ex. 1002, Serels Decl. at ¶ 48, 56, 68; Ex. 1073, Mahalingam Decl. ¶¶ 48, 56, 68.

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. Ex. 1002, Serels Decl. at ¶¶36, 45, 49; Ex. 1073, Mahalingam Decl. ¶¶ 36, 45, 49. The prior art also taught that the combination of ketoconazole and

prednisone was a safe and effective treatment for refractory metastatic prostate cancer. Ex. 1002, Serels Decl. at ¶¶35, 48; Ex. 1073, Mahalingam Decl. ¶¶ 35, 48.

One of skill in the art would have combined abiraterone acetate and prednisone based on 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. Ex. 1002, Serels Decl. at ¶¶48, 49; Ex. 1073, Mahalingam Decl. ¶¶ 48, 49.

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.” Ex. 1008 at p. 2. They further argued that commercial success of Zytiga® (the trade name under which abiraterone acetate is marketed) was evidence of non-obviousness of the claimed combination. Ex. 1008 at pp. 2-3.

However, Gerber taught that some patients with hormone refractory metastatic prostate cancer could derive significant benefit from treatment with ketoconazole and prednisone. Ex. 1002, Serels Decl. ¶35; Ex. 1073, Mahalingam

Decl. ¶ 35. 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. Ex. 1002, Serels Decl. ¶¶31-32, 34, 68; Ex. 1073, Mahalingam Decl. ¶¶ 31-32, 34, 68. The Examiner did not cite Gerber during prosecution. Quite possibly, this is because Gerber was submitted *after* the initial notice of allowance, along with dozens of other references. It appears that 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. Ex. 1012 at p. 6. For example, in traversing repeated obviousness rejections over Tannock (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 the same cancer agent in combination with prednisone.” Ex. 1012 at p. 6.

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 in a clinically significant way, 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 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 claimed 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 same purpose, treating prostate cancer, would be considered *prima facie* obvious.” Ex. 1011 at p. 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 in a clinically significant way.

Moreover, the Examiner committed error in allowing 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 method of treating prostate cancer by administering abiraterone acetate and prednisone) and any commercial success of the drug Zytiga®, which consists of abiraterone acetate.

#### **B. Background of Prostate Cancer and Its Treatment**

Prostate cancer is an androgen-dependent disease. Ex. 1002, Serels Decl. at ¶13; Ex. 1073, Mahalingam Decl. ¶ 13. 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. Ex. 1002, Serels Decl. at ¶14; Ex. 1073, Mahalingam Decl. ¶ 14. The two most important androgens responsible for activating the AR are testosterone and its derivative dihydrotestosterone (“DHT”). Testosterone is synthesized primarily in

the testes and the adrenals.

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. 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. However, a significant number of patients do not respond to localized therapy to suppress testosterone, and consequently develop metastatic prostate cancer. Ex. 1002, Serels Decl. at ¶16; Ex. 1073, Mahalingam Decl. ¶ 16.

The treatment of metastatic prostate cancer requires systemic therapy. An important goal in treating metastatic prostate cancer patients who have undergone localized androgen ablation is to reduce baseline circulating testosterone levels. A substantial amount of extratesticular testosterone is produced in the adrenal glands. The first-line treatment for metastatic prostate cancer patients since at least the 1980's has involved systemic suppression of extratesticular testosterone production by the peripheral organs, including the adrenal glands, and is commonly referred to as hormone therapy. Ex. 1002, Serels Decl. at ¶18; Ex. 1073, Mahalingam Decl. ¶ 18.

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. Ex. 1002, Serels Decl. at ¶21; Ex. 1073, Mahalingam Decl. ¶ 21.

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. Ex. 1002, Serels Decl. at ¶22; Ex. 1073, Mahalingam Decl. ¶ 22.

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. Ketoconazole, a non-specific inhibitor of 17- $\alpha$  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. Ex. 1002, Serels Decl. at ¶23; Ex. 1073, Mahalingam Decl. ¶ 23.

Like ketoconazole, abiraterone is a CYP17 inhibitor. Ex. 1003, (O’Donnell); Ex. 1002, Serels Decl. at ¶¶36, 45; Ex. 1073, Mahalingam Decl. ¶¶ 36, 45. CYP17 inhibitors were known to inhibit CYP17, an enzyme that is critical to androgen synthesis in both the testes and the adrenal cortex. 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. Ex. 1002, Serels Decl. at ¶28; Ex. 1073, Mahalingam Decl. ¶ 28.

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. This results in the pituitary gland producing more adrenocorticotrophic hormone (“ACTH”) to stimulate greater production of glucocorticoids, which are formed from ACTH, in part, by a reaction involving CYP17. However, in the presence of a CYP17 inhibitor, the conversion in the CYP17 pathway from ACTH to cortisol cannot occur. Ex. 1002, Serels Decl. at ¶30; Ex. 1073, Mahalingam Decl. ¶ 30.

It was known that CYP17 inhibition of cortisol increased ACTH drive (*i.e.*, increased ACTH production), which resulted in a corresponding increase in mineralocorticoids. 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. Ex. 1002, Serels Decl. at ¶31; Ex. 1073, Mahalingam Decl. ¶



31. 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. Ex. 1002, Serels Decl. at ¶32; Ex. 1073, Mahalingam Decl. ¶ 32. 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 primary purpose of reducing the side effects associated with increased ACTH drive that result from the CYP17 inhibitor, rather than treating prostate cancer itself. Ex. 1002, Serels Decl. at ¶34; Ex. 1073, Mahalingam Decl. ¶ 34.

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. Ex. 1002, Serels Decl. at ¶34; Ex. 1073, Mahalingam Decl. ¶ 34. Therefore, it was standard practice in the art to co-administer a glucocorticoid when using ketoconazole to treat patients with refractory metastatic prostate cancer. Ex. 1002, Serels Decl. at ¶34; Ex. 1073, Mahalingam Decl. ¶ 34.

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. One of skill in the art would therefore have appreciated that the co-administration of prednisone with abiraterone was not intended to enhance the anti-cancer effect of abiraterone. 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. Ex. 1002, Serels Decl. at ¶34; Ex. 1073, Mahalingam Decl. ¶ 34.

### C. Prior Art References

#### 1. 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 17 $\alpha$ -hydroxylase/C17-20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer,” *British J. of Cancer*, 90:2317-2325 (2004), (“O'Donnell,” “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 teach that abiraterone acetate is a CYP17 inhibitor that suppresses testosterone synthesis in patients with prostate cancer. *Abstract*.

O'Donnell report 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 teach 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.,* Ex. 1003, O'Donnell, *Abstract*; p. 2324. O'Donnell also report that adrenocortical suppression (*i.e.*, suppression of cortisol) may necessitate concomitant administration of replacement glucocorticoid with abiraterone acetate. *Id.*

O'Donnell report 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. Ex. 1003 at p. 2317. O'Donnell explain that this baseline circulating testosterone can activate overexpressed androgen receptors in hormone refractory tumors. Ex. 1003 at p. 2317. O'Donnell also describe ketoconazole as an inhibitor of CYP17 that has shown anti-cancer activity for prostate cancer by decreasing the production of adrenal steroids. O'Donnell also describe abiraterone acetate as a more selective CYP17 inhibitor than ketoconazole of the CYP17 enzyme, which will more effectively decrease the production of adrenal steroids. Ex. 1003 at p. 2318. They further report 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.

Ex. 1003 at p. 2318.

O'Donnell describe the potential utility of abiraterone acetate as an effective anti-cancer agent for treating both castrate and noncastrate patients with advanced prostate cancer. O'Donnell report the results of three separate phase I studies wherein 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. Ex. 1003 at pp. 2322-2323.

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. Ex. 1003 at p. 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. They further report that at 500 mg of abiraterone acetate, treated patients showed persistent reductions in testosterone levels. Ex. 1003 at p. 2323.

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

In addition, O'Donnell report that repeated treatment of noncastrate 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. Ex. 1003 at pp. 2320-2322.

O'Donnell further report 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. Ex. 1003 at p. 2323.

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

1003 at p. 2323.

**2. 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 cancer,” *J. Urol.*, 144(5):1177-9 (November 1990), (“Gerber,” “Ex. 1004”), published 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 November 1990, 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. Therefore Gerber was of record, but not asserted by the Examiner nor argued by the Applicants, during prosecution of the ‘438 patent.

Gerber describe ketoconazole as a potent inhibitor of gonadal and adrenocortical steroid synthesis. Gerber also describe that cytotoxic effects of ketoconazole on prostate cancer cells are known in the art and suggests its potential role in the treatment of prostate cancer. Ex. 1004 at p. 1177.

Gerber teach 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. In particular, Gerber teach that patients with progressive prostate cancer despite androgen

ablation, and therefore unresponsive to initial hormonal therapy, may benefit from the combination of ketoconazole and prednisone. Ex. 1004 at p. 1179.

Gerber note that the results of their study (which combined daily administration of 600-900 mg ketoconazole with the administration of 5 mg prednisone twice daily) show 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. Ex. 1004 at pp. 1178-79. In addition, they report 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. Ex. 1004 at p. 1178-79. They further report that 20% (3 out of 15) patients experienced a prolonged (8 to 10 months) favorable response to ketoconazole and prednisone based on persistently decreasing PSA levels and symptomatic improvement, including improvement in bone pain. Ex. 1004 at pp. 1178-79. Gerber further report that this rate of response is similar to that found in studies that have used changes in measurable tumor size, bone scan abnormalities and acid phosphatase to assess response. Gerber thus conclude that their results show that some patients with progressive prostate cancer despite previous hormone therapy will derive significant benefit from the combination of ketoconazole and glucocorticoid replacement therapy. Ex. 1004 at p. 1179.

**3. In 1997, the ‘213 Patent Disclosed Abiraterone Acetate, and Its Superiority over Ketoconazole in the Treatment of Prostate Cancer**

U.S. Patent 5,604,213, issued to Barrie S.E. *et al.*, “Steroid dependent cancers such as prostate and breast cancer,” (“the ‘213 patent,” Ex. 1005), was published 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 on February 18, 1997, 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 incorporated by reference in the ‘438 patent, but it was neither argued nor disclosed in an IDS as relevant prior art during prosecution.

The ‘213 patent is one of the patents listed in the FDA 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 was neither argued nor disclosed to the PTO in an IDS during prosecution.

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. Ex. 1005 at Col. 1, ll. 11-14. The compounds of the ‘213 patent include abiraterone and acid addition salts and 3-esters of abiraterone (*see, e.g.*, Ex. 1005 at Col. 5, ll. 21- 26; Example



2 at col. 11, ll. 39-55), as well as abiraterone acetate in particular (*see, e.g.*, Ex. 1005 at Example 1 at col. 10, ll. 62-11:35).

The '213 patent further discloses 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 discloses to be 20-800 mg/patient per day of abiraterone acetate. Ex. 1005 at Col. 10, ll. 27-57.

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

The '213 patent reports results from in vitro inhibition assays using tissue from the testes of previously untreated human patients undergoing orchidectomy for prostatic cancer. The assays compare the in vitro inhibition of  $17\alpha$ -hydroxyprogesterone androstenedione and testosterone production by some of the compounds of the invention, including abiraterone acetate (i.e., Example 1) with that of ketoconazole. The reported  $IC_{50}$  for abiraterone acetate is 0.0097 against lyase and 0.0130 against hydroxylase. By comparison, the reported  $IC_{50}$  for

ketoconazole is 0.026 against lyase (or an order of magnitude higher than abiraterone acetate) and 0.065 against hydroxylase. Ex. 1005 at Col. 21, l. 25-25, l. 12.

The '213 patent further disclose the results of in vivo assays involving male human wild type ("HWT") mice that compare the effect on organ weight and production of testosterone and luteinizing hormone of administering abiraterone acetate and ketoconazole, respectively. 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. 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. Ex. 1005 at Col. 25, l. 41 - 26, l. 25; Table 3.

The '213 patent conclude that mammalian assays show that abiraterone acetate inhibits androgen, and particularly testosterone, synthesis. Ex. 1005 at Col. 26, ll. 27-63; Table 4. The '213 patent further conclude that the decrease in testosterone levels resulting from the administration of abiraterone acetate was much more marked than for ketoconazole. Ex. 1005 at Col. 26, ll. 32-38.

## **XII. EXPLANATION OF GROUNDS FOR UNPATENTABILITY**

### **A. Claim 1**

Claim 1 is obvious over O'Donnell in view of Gerber (Ground 1) or the

'213 Patent in view of Gerber (Ground 2). 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 administration of therapeutically effective amounts of abiraterone acetate, or a pharmaceutically acceptable salt thereof, and prednisone. Because both the use of abiraterone acetate to treat prostate cancer and the co-administration of prednisone in treatment of prostate cancer with a CYP17 inhibitor were present in the prior art with sufficient motivation to combine, claim 1 is obvious.

With respect to abiraterone acetate, both O'Donnell and the '213 patent teach that abiraterone acetate is a selective CYP17 inhibitor that is more effective in suppressing testosterone levels in a mammal *in vivo* than ketoconazole, a CYP17 inhibitor known in the art. Ex. 1003, O'Donnell, at pp. 2318, 2322, 2323; 2325; Exhibit 1005, the '213 patent, col. 25, l. 13 - col. 26, l. 63. O'Donnell teach 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. Ex. 1003, O'Donnell, *Abstract*. The '213 patent discloses that abiraterone acetate may be administered in a method of treating androgen- and estrogen-dependent disorders, especially prostate cancer, as a pharmaceutical composition. Ex. 1005, the '213 patent, col. 10, ll. 47-56. The '213 patent further discloses that a therapeutically effective amount of abiraterone acetate comprises 20-800 mg/patient

per day. Ex. 1005, the '213 patent, col. 10, ll. 55-56. The '213 patent also teaches that a salt of abiraterone acetate may be administered to a human patient with prostate cancer to treat prostate cancer in said human patient. Ex. 1005, the '213 patent, col. 10, ll. 22-26.

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

Neither O'Donnell nor the '213 patent disclose co-administering prednisone with abiraterone acetate.

Although O'Donnell does not disclose administration of abiraterone acetate with prednisone, O'Donnell teaches that concomitant hormone replacement therapy with a glucocorticoid may be needed for continuous use of abiraterone acetate in treating a prostate cancer in a human patient. *See, e.g.*, Ex. 1003, O'Donnell, *Abstract*, p. 2323. Gerber teaches that the combination of ketoconazole and prednisone is safe and effective in treating human patients with hormone-refractory advanced prostate cancer. Exhibit 1005, Gerber, *Abstract*, pp. 1177-1178, 1179. The motivation to add prednisone to a method of treating prostate cancer in a human patient that includes abiraterone acetate is clearly seen in Gerber 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. Ex. 1004, Gerber, *Abstract* pp. 1177-1178, 1179.

As such, the skilled artisan would expect that the addition of 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 teaches that abiraterone acetate is a CYP17 inhibitor that is more effective in suppressing testosterone levels in a mammal in vivo than ketoconazole, a CYP17 inhibitor known in the art. Ex. 1005, the '213 patent, col. 25, l. 13 - col. 26, l. 63. Gerber teaches that the combination of ketoconazole and prednisone is safe and effective in treating human patients with hormone-refractory advanced prostate cancer. Ex. 1004, Gerber, *Abstract*, pp. 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. Ex. 1004, Gerber, *Abstract* pp. 1177- 1178, 1179. As such, the skilled artisan would expect that the addition of 5 mg twice daily prednisone to the treatment regimen of the '213 patent also would be safe and

effective in treating a prostate cancer, including prostate cancer refractory to anti-cancer therapy, including hormone and anti-androgen therapy, in such patients.

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/daily of prednisone with abiraterone acetate, a more selective CYP17 inhibitor than ketoconazole, in order 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.

Claims 2-20 all depend directly or indirectly from claim 1, and include additional limitations of combinations 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; or 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. For the reasons set forth above for claim 1 and additionally for the reasons set forth below, these additional categories of limitations also are obvious over O'Donnell in view of Gerber and/or the '213 patent in view of Gerber.

**B. Claims 2 and 3**

O'Donnell teaches that 500-800 mg of abiraterone acetate can be useful in suppressing testosterone levels in a human patient with prostate cancer, including metastatic prostate cancer. *See, e.g.*, Ex. 1003, O'Donnell, *Abstract*. The '213 patent teaches that a therapeutically effective amount of abiraterone acetate for treating prostate cancer in a human patient includes 20-800 mg/day. 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 of 20-800 mg per day of abiraterone acetate as expressly taught in the '213 patent is within the range of “about 50 mg/day to about 2000 mg/day” (claim 2); and “about 500 mg/day to about 1500 mg/day” (claim 3). For the foregoing reasons, the daily dosage amounts and ranges of abiraterone acetate recited in these claims are disclosed both in O'Donnell and the '213 patent.

Therefore claims 2 and 3 are obvious over O'Donnell in view of Gerber (Ground 1) or the '213 patent in view of Gerber (Ground 2).

**C. Claim 4**

Although neither O'Donnell nor the '213 patent expressly teach an amount of abiraterone acetate of about 1000 mg/day as recited in claim 4, O'Donnell reports a dose of 500-800 mg/day of abiraterone acetate used in phase 1 human studies. Ex. 1003, *Abstract*, p. 2318. The '213 patent discloses 20-800 mg/day of

the drug. Ex. 1005, the '213 patent, Col. 10, ll. 55-56. O'Donnell reports 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 luteinizing hormone ("LH"). Ex. 1003, O'Donnell, *Abstract*. O'Donnell concludes from the studies that in the face of increased LH, higher doses of abiraterone acetate may be required. *See, e.g.,* Ex. 1003, O'Donnell, *Abstract*; p. 2324.

It would have been obvious to one of skill in the art to optimize the dosage range of abiraterone acetate to 1000 mg administered to treat prostate cancer in a human patient based on the teaching in O'Donnell 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 of known active ingredients to be administered was considered well within the competence level of an ordinary skilled artisan in the pharmaceutical sciences as of at least 2006.

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.

**D. Claim 5**

O'Donnell teaches that capsules containing 10, 50, 100 and 200 mg of



abiraterone acetate were used in the three phase 1 clinical studies. It would have required only routine experimentation to increase the amount of abiraterone acetate in the capsules from 200 mg to 250 mg. 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, which are a multiple of 250 mg. Therefore one of skill in the art would have made a 250 mg dosage form of abiraterone acetate for the convenience of dosing. For at least this reason claim 5 is obvious over O'Donnell in view of Gerber.

**E. Claims 6-9**

Claims 6-9 are directed to the amount or range of amount of prednisone administered: “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). Each of these limitations is disclosed in Gerber, which teaches 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. Ex. 1004, Gerber, *Abstract*, pp. 1177-1178, 1179.

Claim 6 depends from claim 1 and is obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 is obvious and further for the disclosure in Gerber of 10 mg/day of prednisone.

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

Claim 8 depends from claim 7 and narrows the range to about 10 mg/day of prednisone. Because Gerber discloses 10 mg/day of prednisone, claim 8 is obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 is obvious and further for the disclosure in Gerber of 10 mg/day of prednisone.

Claim 9 depends from claim 1 and requires the dosage form of prednisone to be about 5 mg. Gerber discloses administering 5 mg of prednisone twice daily, a dosage form of 5 mg of prednisone would have been obvious. As such, claim 9 is obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 is obvious and further for the disclosure in Gerber of administering 5 mg of prednisone.

**F. Claim 10**

Claim 10 depends from claim 1 and includes the limitation 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. These limitations are recited in claims 3 and 6

respectively. Therefore claim 10 is 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.

**G. Claim 11**

Claim 11 depends from claim 10 and includes the limitations of about 1000 mg/day of abiraterone acetate and about 10 mg/day of prednisone. These limitations are recited in claims 4 and 8 respectively. Therefore claim 11 is 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.

**H. Claims 12-16**

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, foserelin, 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. Ex. 1001, O'Donnell,

*Abstract*, pp. 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. Ex. 1003, O'Donnell, *Abstract*; pp. 2318-2319, 2320. In Study A, all patients had received flutamide, an anti-androgen agent recited in claim 16, and were receiving goserelin or leuprorelin, hormone ablation agents. Therefore claims 12 and 13 are obvious for the reasons set forth for claim 1 and additionally for the teaching in O'Donnell 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.

Claim 14 is obvious for the reasons set forth for claims 1, 12 and 13 and additionally for the teaching in O'Donnell that all three cohorts of patients in O'Donnell had previously undergone hormone or anti-androgen therapy or both.

Claim 15 is obvious for the reasons set forth for claims 1, 12, 13 and 14 and additionally for the teaching in O'Donnell that the patients in Study A had previous undergone hormone ablation therapy with goserelin or leuprorelin.

Claim 16 is obvious for the reasons set forth for claims 1, 12, 13 and 14 and additionally for the teaching in O'Donnell that the patients in Study A had

previous undergone anti-androgen therapy with flutamide.

**I. Claim 17**

Claim 17 depends from claim 14 and includes the limitations that the anti-neoplastic agent is docetaxel. O'Donnell does not expressly teach that abiraterone acetate may be administered to treat a human patient with metastatic prostate cancer that is refractory to an anti-neoplastic agent comprising docetaxel.

However, 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 (Ex. 1029) which issued on November 18, 1997, states at col. 2, ll. 29-32, that docetaxel is an anti-cancer compound. And docetaxel in combination with prednisone was known to increase overall survival of patients with metastatic refractory prostate cancer, (Ex. 1022, Tannock, Abstract), the first treatment known to do so, and was approved for the treatment of metastatic refractory prostate in 2004. *See*, Ex. 1030, FDA News Release dated May 19, 2004. Therefore, claim 17 is obvious over O'Donnell in view of Gerber for the reasons set forth for claim 14 and additionally for the general knowledge in the art that docetaxel with prednisone was a first-line treatment for metastatic hormone refractory prostate cancer known to increase overall survival.

**J. Claim 18**

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. Therefore claim 18 is invalid as being obvious over O'Donnell in view of Gerber for the reasons set out above for claims 10 and 12.

**K. Claim 19**

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. Therefore claim 19 is invalid as being obvious over O'Donnell in view of Gerber for the reasons set out above for claims 11 and 18.

**L. Claim 20**

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. Therefore claim 20 is invalid as being obvious over O'Donnell in view of Gerber for the reasons set out above for claims 11 and 17.

**XIII. SECONDARY CONSIDERATIONS DO NOT INDICATE THAT THE CLAIMS OF THE '438 PATENT ARE NON-OBVIOUS**

To counter the *prima facie* evidence that all claims of the '438 patent are obvious, the patentee may try to rely on secondary considerations of non-obviousness. While any such evidence would be “insufficient” to “overcome the strong case of obviousness” here (*Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2008)), we nonetheless preliminarily address these alleged secondary

considerations below, and reserve the right to respond to any arguments by the patentee asserted in this proceeding.

**A. 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 commercial success of Zytiga®, the commercial product containing abiraterone acetate, was evidence of the non-obviousness of the claimed invention. Ex. 1012 at p. 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. Ex. 1013, Ex. 1014, Ex. 1015. This was in error.

It is well settled that evidence of secondary considerations, such as commercial success, is only relevant to an obviousness analysis if the Patentees can show a direct link, or nexus, between the secondary consideration and the claims of the patent. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 305 n.42, 227 USPQ 657, 673-674 n. 42 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). In addition, that 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 Technologies, Inc.*, Case Nos. IPR 13-00097 and IPR 13-00102 (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(I).

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. Ex. 1012 at p. 7, slide 12. Even assuming that the market definition Applicants used is accurate (and it is 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®. In addition, as Dr. McDuff explains, evidence of Zytiga's® purported market share in a market Applicants define as the “post-chemo” mCRPC therapeutic market is deficient for a number of reasons. First, Applicants adduced no evidence that a market consisting only of “post chemo” mCRPC patients is the appropriate relevant market. As Dr. McDuff explains in his declaration, this market definition is much too narrow. Ex. 1017, McDuff Decl. at ¶¶23-26. Using a market definition that includes all mCRPC patients immediately reduces Zytiga’s market share substantially. Ex. 1017, McDuff Decl. at ¶¶24-25.

Second, recent market data demonstrate a steep and continuous decline in Zytiga’s market share post-Xtandi launch, and concurrent growth in Xtandi market share. Ex. 1017, McDuff Decl. at ¶¶27-29. Dr. Serels explains that the perception



among clinicians is that Xtandi has similar efficacy to, but a better safety profile than, Zytiga because Xtandi does not require co-administration of prednisone. Ex. 1002, Serels Decl. at ¶¶85-87; Ex. 1073, Mahalingam Decl. ¶¶ 85-87. The superior safety of Xtandi may account for Xtandi's growth in market share. In any event, this market shift is particularly notable in light of Applicants' argument during prosecution that Zytiga's continued commercial success after the introduction of Xtandi was further evidence of the commercial success of the invention. Ex. 1017, McDuff Decl. at ¶¶23-30.

Lastly and most importantly, even assuming *arguendo*, that Zytiga's commercial performance, regardless of how broadly the relevant therapeutic market is defined, has been strong, any commercial success of Zytiga® is not shown to derive from the claimed invention, i.e., the combination of abiraterone acetate and prednisone. Ex. 1017, McDuff Decl. at ¶¶31-35. Certainly, Applicants made no effort during prosecution to show any nexus between the claimed invention and the commercial performance of Zytiga®. Instead, any commercial success of Zytiga® is likely due to the effectiveness of abiraterone acetate 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 mislead the Examiner by

arguing that because Zytiga® is approved in combination with prednisone, Zytiga® is a commercial embodiment of the claimed invention. Ex. 1012 at p. 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.

**B. One of Skill 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. Serels

explains, the anti-cancer effect of administering Zytiga® to treat prostate cancer is obtained from abiraterone acetate. Ex. 1002, Serels Decl. at ¶84; Ex. 1073, Mahalingam Decl. ¶ 84. 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*. Ex. 1002, Serels Decl. at ¶¶68-70, 74-78; Ex. 1073, Mahalingam Decl. ¶¶ 68-70, 74-78. 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. Ex. 1002, Serels Decl. at ¶¶74, 80; Ex. 1073, Mahalingam Decl. ¶¶ 74, 80.

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. Ex. 1002, Serels Decl. at ¶¶36, 45; Ex. 1073, Mahalingam Decl. ¶¶ 36, 45. For example, abiraterone acetate for the treatment of prostate cancer was disclosed and claimed in the '213 patent. Ex. 1002, Serels Decl. at ¶¶36, 45, 73; Ex. 1073, Mahalingam Decl. ¶¶ 36, 45, 73. Abiraterone acetate had been shown to reduce testosterone levels in refractory metastatic prostate cancer patients in clinical trials.

Ex. 1002, Serels Decl. at ¶¶36, 45; Ex. 1073, Mahalingam Decl. ¶¶ 36, 45. 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*.

But Applicants never once argued unexpected results of administering abiraterone and prednisone over abiraterone alone. Instead, Applicants mislead the Examiner by arguing alleged unexpected benefits of abiraterone and prednisone over prednisone and a placebo. *See e.g.*, July 3, 2012 Response (Ex. 1008), January 11, 2013 Response (Ex. 1010); June 4, 2013 Response (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.

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. Ex. 1002, Serels Decl. at ¶¶75-78; Ex. 1073, Mahalingam Decl. ¶¶ 75-78. Instead, in 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. Ex. 1018, 2011 Zytiga® Approval Prescribing Information, at pp. 3-4, 5-6, 11; Ex. 1019, 2015 Zytiga® Prescribing Information, Co-administration Brochure, at pp. 2-3.

For example, the 2015 brochure “Putting Prednisone in Perspective,” that accompanies the 2015 revised Prescribing Information for Zytiga®, states that “prednisone reduces the incidence and severity of mineralocorticoid-related adverse reactions associated with Zytiga®” and that “coadministration [sic] of prednisone [with Zytiga®] suppresses the ACTH drive and reduces the incidence and severity of mineralocorticoid excess adverse reactions.” Ex. 1019, 2015 Zytiga® Prescribing Information, Co-administration Brochure, at p. 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.” Ex. 1019, 2015 Zytiga® Prescribing Information, Co-administration Brochure, at p. 3.

As Dr. Serels and Dr. Mahalingam explain in the accompanying declarations, it was known in the art that administering ketoconazole, also 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. Ex. 1002, Serels Decl. at ¶¶34, 68-70; Ex. 1073, Mahalingam Decl. ¶¶ 34, 68-70. These adverse effects reduced the safety of administering ketoconazole as a single agent. Ex. 1002, Serels Decl. at ¶¶34, 68-70; Ex. 1073, Mahalingam Decl. ¶¶ 34, 68-70. 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. Ex. 1002, Serels Decl. at ¶¶35, 68-70; Ex. 1073, Mahalingam Decl. ¶¶ 35, 68-70. 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*; Ex. 1002, Serels Decl. at ¶¶48-49, 68-70; Ex. 1073, Mahalingam Decl. ¶¶ 48-49, 68-70.

Based on at least these teachings, one of skill in the art would have had a reasonable expectation that administration of abiraterone, a more selective CYP17 inhibitor than 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. Ex. 1002, Serels Decl. at ¶¶48-49, 68-70; Ex. 1073, Mahalingam Decl. ¶¶ 48-49, 68-70.

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. *See, e.g.*, Ex. 1004, Gerber, *Abstract*, pp. 1178-1179; Ex. 1020, Harris, p. 544; Ex. 1021, Oh, *Abstract*, p. 90; Ex. 1003, O'Donnell, p. 2323; Ex. 1002, Serels Decl. at ¶¶68-70, 74, 80; Ex. 1073, Mahalingam Decl. ¶¶ 68-70, 74, 80.

**C. 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. McDuff, any success of Zytiga® that is not a result of the claimed invention is irrelevant to secondary considerations. Ex. 1017, McDuff Decl. at ¶¶31-35. As Dr. Serels explains, the combination of abiraterone acetate and prednisone does not produce unexpected results in anti-cancer benefit. Ex. 1002, Serels Decl. at ¶¶74, 80, 83; Ex. 1073, Mahalingam Decl. ¶¶ 74, 80, 83. 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. Ex. 1002, Serels Decl. at ¶85; Ex. 1073, Mahalingam Decl. ¶ 85. For at least these reasons, the combination of abiraterone and prednisone satisfied no long-felt need beyond what abiraterone may have done.

**D. 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 Pharmaceuticals 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. Ex. 1002, Serels Decl. ¶¶36, 45, 73; Ex. 1073, Mahalingam Decl. ¶¶ 36, 45, 73. The FDA’s Orange Book lists the ‘213 patent as covering Zytiga®<sup>3</sup>. 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. 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

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<sup>3</sup> 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](http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202379&Product_No=001&table1=OB_Rx) (accessed 07/24/2015).



relevance of commercial success for the '438 patent. Ex. 1017, McDuff Decl. at ¶¶18-20.

As Dr. McDuff 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. Ex. 1017, McDuff Decl. at ¶¶16-17. A finding of commercial success can, in some circumstances, support the notion that a patent was not obvious to those skilled in the art if those incentives for development existed. Ex. 1017, McDuff Decl. at ¶17. However, in this case, the '213 patent was a blocking patent that limited economic incentives to develop the invention of the '438 patent. Ex. 1017, McDuff Decl. at ¶¶18-20. As Dr. McDuff explains, “Because Johnson & Johnson could have effectively prevented market participants from supplying an abiraterone product, typical incentives associated with drug development would not have existed.” Ex. 1017, McDuff Decl. at ¶20.

#### **E. Copying By Generic Drug Makers Is Irrelevant**

Finally, the Patentees may argue that Petitioners 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).

### **XIII. 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 29, 2016

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**CERTIFICATION OF WORD COUNT**

Pursuant to 37 C.F.R. §§ 42.24, the undersigned certifies that the argument section of this Petition (Sections I-XIV) has a total of 13,342 words, according to the word count tool in Microsoft Word™.

Respectfully submitted,

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**CERTIFICATE OF SERVICE**

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), the undersigned certifies that on June 29, 2016, a complete copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,822,438, Power of Attorney, and all supporting exhibits were served via FedEx® on the Patent Owner by serving the correspondence address of record for the '438 Patent:

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Courtesy copies of the foregoing were also served via email on the counsel of record for the Petitioner and Patent Owner in *Amerigen Pharmaceuticals Ltd. v. Janssen Oncology, Inc.*, IPR2016-00286 as follows:

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