UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

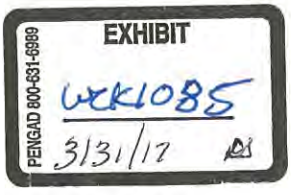
MYLAN PHARMACEUTICALS INC.
Petitioners,

v.

JANSSEN ONCOLOGY, INC.
Patent Owner.

Case IPR2016-01332
Patent 8,822,438 B2

**DECLARATION OF MATTHEW B. RETTIG, M.D.
IN SUPPORT OF JANSSEN ONCOLOGY, INC.'S
PATENT OWNER RESPONSE**



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I, Matthew B. Rettig, M.D., hereby declare as follows:

I. INTRODUCTION

A. Engagement

1. I have been retained by counsel for Patent Owner Janssen Oncology Inc. ("Janssen") to provide expert and testimony as background for the panel of Administrative Patent Judges of the Patent Trial and Appeal Board of the United States Patent and Trademark Office ("Panel") as it considers issues relating to the patentability of U.S. Patent No. 8,822,438 (the '438 Patent) (Ex. 1001) in an *inter partes* review requested by Mylan Pharmaceuticals, Inc. (hereinafter "Mylan") in Case No. IPR2016-01332.

B. Background and Qualifications

2. I am Medical Director of the Prostate Cancer Program of the Institute of Urologic Oncology at the David Geffen School of Medicine at the University of California, Los Angeles ("UCLA School of Medicine"). I am also Professor in the Department of Medicine and the Department of Urology at the UCLA School of Medicine. I am also Chief of the Division of Hematology-Oncology for the Veteran's Administration (VA) Greater Los Angeles Healthcare System in West Lost Angeles. In addition, I serve as the Director of the Operation Mend Project to Enhance Cancer Care for Veterans, a collaboration between UCLA and the VA Greater Los Angeles Healthcare System to enhance cancer care for veterans.

3. I received my Bachelor's degree in Chemistry from Wesleyan University in 1986, and my M.D. from the Duke University School of Medicine in 1990. I have been in active medical practice since 1991, including an internship in internal medicine at the University of Southern California, Los Angeles, a residency in internal medicine at the University of Washington, Seattle, and a fellowship in hematology/oncology at the UCLA School of Medicine. I was Board Certified in internal medicine in 1991 and have been Board Certified in oncology since 1998.

4. I have both clinical and laboratory research programs. As the director of the clinical trials program in prostate cancer at UCLA, I conduct multiple prostate cancer clinical trials that span the spectrum of the states of the disease, from neoadjuvant therapies to post-chemotherapy, castration-resistant disease. My laboratory research program, which includes programs funded by the NIH, Prostate Cancer Foundation, American Cancer Society, Department of Defense, and the Department of Veterans Affairs, is focused on identifying biochemical targets for drug development in castration-resistant prostate cancer and kidney cancer. I have been the recipient of fifty research grants and fellowships, including nineteen that are currently active, most relate to prostate cancer.

5. In addition to my medical practice, I serve on a number of advisory committees relating to oncology and urology. For example, I am a full-time

member of the VA Merit Review Oncology A Study Section (Genitourinary Prostate Cancer Section), a Director for the Multidisciplinary Tumor Board for VA-West LA, a grant reviewer for the Prostate Cancer Foundation and the Tower Cancer Research Foundation, and Chairman of the Board of Directors for the Brentwood Biomedical Research Institute (a non-profit grant-making organization at VA). I am also co-Chairman of the steering committee of the Prostate Cancer Foundation ("PCF")-VA Strategic Partnership (known as the Precision Oncology Program Cancer of the Prostate ("POPCAP") which is part of Vice President Joseph Biden's National Cancer Moonshot effort, overseeing $50 million in research funding over the next five years.

6. I am a recipient of multiple awards, including Creativity Award from the Prostate Cancer Foundation (2010, 2011), a Challenge Award, Prostate Cancer Foundation (2012), STOP Cancer Award, Jerry Janger Memorial Seed Grant (2015), and a VALOR Award also from the Prostate Cancer Foundation.

7. I am an author on over fifty peer-reviewed papers that have been published or accepted for publication, many relating to treatment of prostate cancer. A full list of my publications, positions, research grants, and other qualifications is contained in my *curriculum vitae*, Exhibit 2039.

C. Compensation and Prior Testimony

8. I am being compensated at my customary rate of $900/hour for work in connection with this proceeding, such as my study of the '438 patent and the cited prior art. If I travel for more than three hours for this proceeding (and am not otherwise billing time), I am being compensated $2,500 per day. I am also being reimbursed for reasonable and customary expenses associated with my work in this proceeding. My compensation is in no way contingent upon the outcome of this proceeding or the specifics of my testimony.

D. Materials Considered

9. My opinions are based on my approximately thirty years of education, research, and medical practice and experience in the fields of internal medicine and oncology, including my specific experience studying and treating prostate cancer, as well as my investigation and study of the relevant materials. In forming my opinions, I have considered the materials referred to herein and listed in Appendix A.

10. I reserve the right to revise, supplement, and/or amend my opinions based on any new information that I receive and on my continuing analysis of the materials referred to herein and listed in Appendix A. I may also consider additional information in forming my opinions, including documents that I may not yet have reviewed and that have not yet been provided to me.

II. LEGAL STANDARDS REGARDING PATENTABILITY

11. In expressing my opinions and considering the subject matter of the claims of the '438 Patent, I have relied on certain basic legal principles that counsel have explained to me.

12. I understand that for an invention claimed in a patent to be valid and patentable, it must be, among other things, new and not obvious in light of what was known and came before it. That which was known and came before the claimed invention is generally referred to as "prior art."

13. I understand that in this proceeding the burden of proving that the '438 Patent is unpatentable falls on the Petitioners, here Mylan, and must be shown by "preponderance of the evidence." I understand "preponderance of the evidence" to mean evidence sufficient to show that a fact is more likely true than not.

14. I understand that a claimed invention is obvious when the differences between the subject matter patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art ("POSA") to which the subject matter pertains. I understand that a POSA is a hypothetical person who has the characteristics of an ordinary practitioner, including ordinary creativity.

15. I understand that in order to find a patent claim obvious, certain findings regarding the claimed invention and the prior art are required. In particular, I understand that evaluating obviousness requires consideration of four factors: (a) the scope and content of the prior art; (b) the differences between the prior art and the claims at issue; (c) the knowledge of a person of ordinary skill in the pertinent art; and (d) whether objective factors (which may arise later in time from when the invention was made) indicating obviousness or non-obviousness are present in the particular case.

16. I understand objective factors bearing on the question of obviousness or non-obviousness may include: (a) commercial success of products covered by the patent claims; (b) a long-felt need for the invention; (c) skepticism or failed attempts by others to make the invention or solve the problem solved by the invention; (d) copying of the invention by others working in the field; (e) unexpected results achieved by the invention; and (f) the fact that the patentee proceeded contrary to the accepted wisdom of the prior art. For the objective factors to be relevant, I understand that the evidence relating to these factors must have a connection or causal nexus to the subject matter as claimed.

17. I understand that an invention may be considered non-obvious if one or more prior art references discourage or lead away from the subject matter of the invention. I understand that teaching away requires some clear discouragement of

the claimed combination in the prior art. I further understand that the obviousness inquiry should not be performed with the benefit of hindsight. Instead, the inquiry must be performed based on knowledge at the time of the invention.

18. For purposes of this declaration, I have been asked to use August 25, 2006, the earliest effective filing date of the '438 patent, as the relevant date for my analysis. Unless I state otherwise, my opinions in this declaration are made from the perspective of a POSA as of August 25, 2006.

III. TECHNICAL BACKGROUND

A. Control of Prostate Growth and Function by Androgens

1. Prostate growth and function

19. The prostate is a gland of the male reproductive system. The prostate secretes part (~30%) of the seminal fluid that mixes with sperm to become semen. The development and maintenance of the prostate is under the control of male sex steroid hormones known as androgens. Other types of sex steroid hormones include estrogens and progestins. Non-sex steroids include (among others) glucocorticoids and mineralocorticoids, both of which are produced in the adrenal glands. (Ex. 2058 (Seifter) at 540-47; Ex. 2086 (Princip. Endoc. Ch. 72) at 705).

20. The principal androgen in men is testosterone. Testosterone is derived from cholesterol, the physiologic substrate of all steroids. Besides testosterone, the other principal androgens are dehydroepiandrosterone (DHEA) and androstenedione, which have weak androgenic activity. DHEA and

androstenedione are converted into testosterone in peripheral tissues such as prostate tissue. (Ex. 2086 (Princip. Endoc. Ch. 72) at 710-11; *see also* Ex. 1003 (O'Donnell) at 2317).

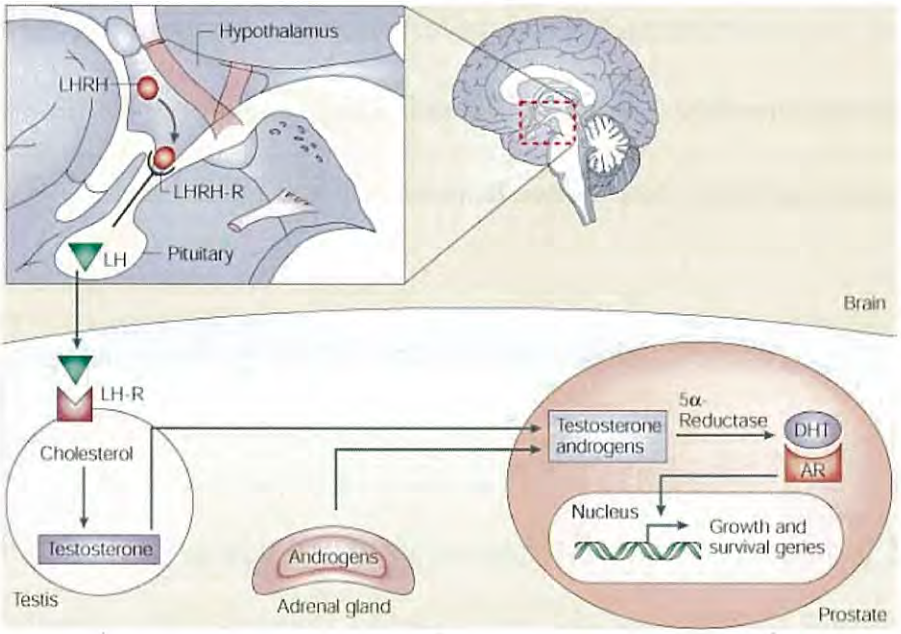
21. In the normal prostate, chronic stimulation with androgens, including testosterone and its potent metabolite, dihydrotestosterone ("DHT"), is required for maintenance of tissue homeostasis and secretory function. (Ex. 1023 (Attard (2005)) at 1241). Androgen deprivation induces programmed cell death (apoptosis) in the prostate cells and results in involution (*i.e.*, shrinkage) of the prostate gland.

22. The major source of androgens in the prostate is the testosterone supplied by the testes through blood circulation (90%). Approximately 10% of androgens originate from the adrenal glands.

23. Testosterone production is regulated by the hypothalamus and anterior pituitary gland. The hypothalamus produces luteinizing hormone-releasing hormone (LHRH), which stimulates the pituitary to synthesize and secrete luteinizing hormone (LH). In the testes, LH induces production of testosterone, which is synthesized from cholesterol. Testosterone acts through a negative feedback loop to decrease LHRH and, in turn, LH production and secretion, thereby maintaining serum testosterone at physiological levels. (Ex. 2058 (Seifter) at 608, Fig. 37.3).

24. Testosterone and DHT exert their biological effects by binding to the androgen receptor (AR), an intracellular protein that plays a critical role in regulating gene expression. Binding of an androgen to the AR initiates a cascade of events that results in regulation of transcription of androgen-responsive genes, which mediate cell growth and differentiation in prostate cells. (Ex. 1023 (Attard (2005)) at 1241). In particular, activation of the AR is critical at least initially for the survival and growth of prostate cancer cells. Figure 1 summarizes the production of testosterone and its action on the prostate:

Figure 1



2. Androgen Synthesis

25. Steroid hormones perform different functions in the body and these functions are based on the steroid receptor to which they bind. Steroids can be

broadly classified as mineralocorticoids (e.g., aldosterone), glucocorticoids (e.g., cortisol and corticosterone), and sex steroids (e.g., estrogens, androgens, and progestins). (Ex. 2086 (Princip. Endocr. Ch. 72) at 705). However, the classification of steroids in a particular class is not absolute; for example, some mineralocorticoids can function as weak androgens.

26. All steroid hormones, including androgens and non-androgen steroids, are derivatives of cholesterol. (Ex. 2058 (Seifter) at 551). The gonads (testes in men) produce only sex steroids, whereas the adrenal glands can produce sex steroids, glucocorticoids, and mineralocorticoids. (*Id.* at 551, 608). The testes are the only organs in men that produce testosterone. Importantly, the adrenal glands produce sex steroids such as DHEA and androstenedione, but do not have the enzymatic capability to produce testosterone and DHT.[1] (Ex. 1003 (O'Donnell) at 2317).

27. Figure 2 below describes the steroid synthesis pathway[2]:

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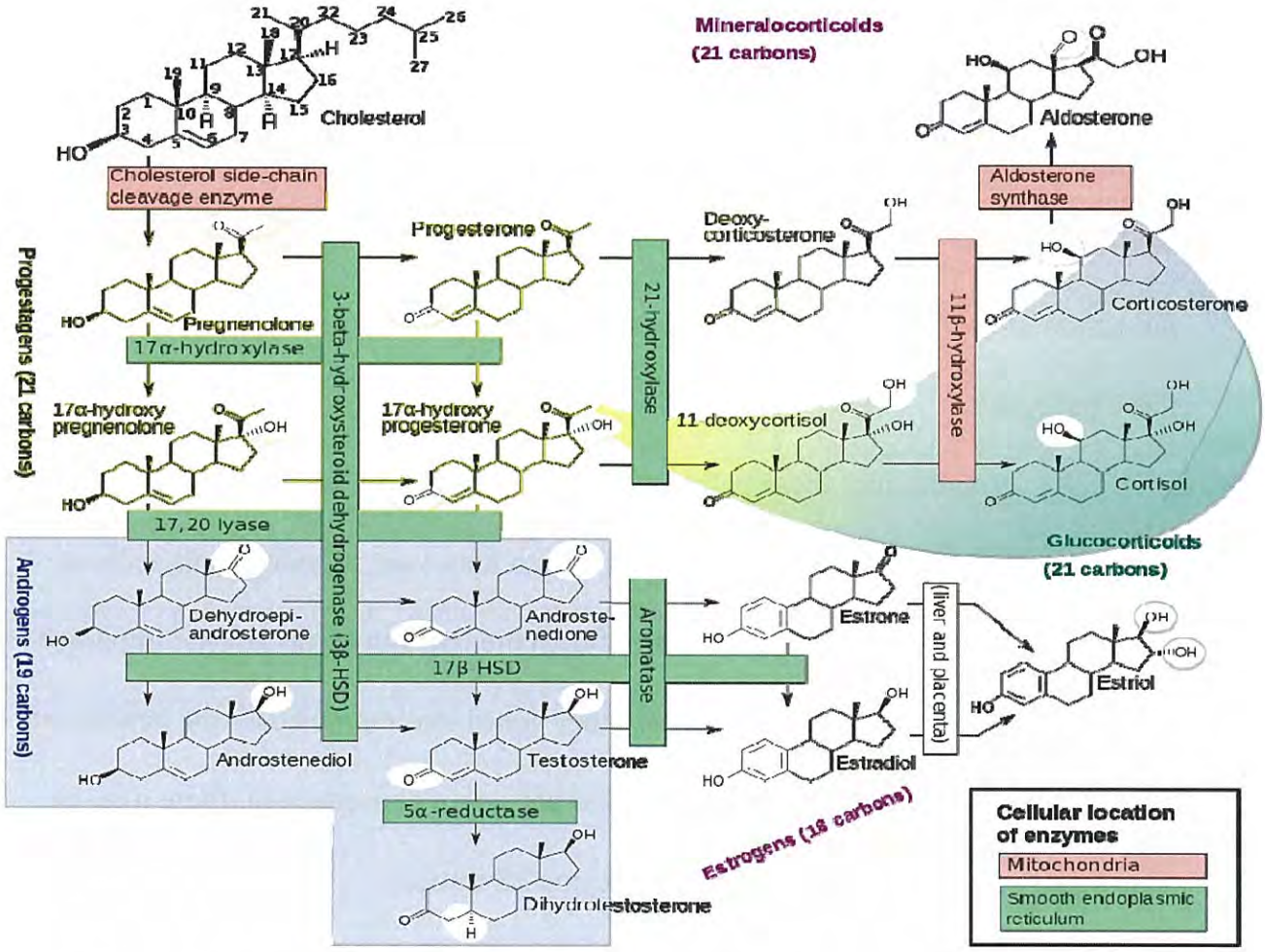
[1] DHT is derived from testosterone in peripheral tissues (including the testes, adrenal glands, and prostate).

[2] The steroid synthesis pathway was well known as of August 2006. (*See e.g.,* Ex. 1003 (O'Donnell); Ex. 2086 (Princip. Endocr. Ch. 72) at 707).

Figure 2



28. In Figure 2, steroid hormones are identified by their names and chemical structures. The steroid synthesis pathway includes dozens of different steroids and their intermediates. (Ex. 2086 (Princip. Endocr. Ch. 72) at 707; Ex. 1003 (O'Donnell) at 2318 Fig. 1). Production of the steroids and intermediates is carefully regulated in response to changing requirements and/or to maintain homeostasis.

29. As can be seen, the steroid synthesis pathway is very complex. Enzymes operate at various steps in the biochemical pathways to regulate the step-by-step biosynthesis of steroids. Figure 2 shows numerous different enzymes, inhibition of which will affect the production of downstream reaction products. While the major reactants and products of each enzymatic reaction are understood, the action of each enzyme can be affected by other enzymes and components of these pathways.

30. In addition, these pathways can be affected by the individual expression and activity of these enzymes, which may vary in individuals without resulting in a disease state. The effects of enzyme inhibition can also be impacted by individual specific factors including other genes that may modify the actions of other enzymes as well as environmental factors. As a consequence, there may be significant variability in the effects of enzyme inhibition.

31. In addition, a number of the steroids have overlapping functions. For example, cortisol has some weak mineralocorticoid activity and, conversely, corticosterone (a weak mineralocorticoid) has some glucocorticoid activity. (Ex. 2058 (Seifter) at 543); Ex. 2086 (Princip. Endocr. Ch. 72) at 710. Thus, these steroids can provide some compensatory function for each other when one is in short supply. An example of this compensatory activity is rescue of cortisol deficiency by corticosterone.

32. As a result of differential enzyme expression and regulation, and the compensatory functions of the steroids, it is not possible to predict in advance whether changes in the levels of steroid synthesis will result in medical symptoms requiring clinical intervention.

33. Figure 2 shows the steps in the production of testosterone and other male hormones from the initial starting point of cholesterol. The first step in this pathway is the production of pregnenolone from cholesterol, which is catalyzed by the enzyme desmolase (also known as side chain cleavage enzyme). (Ex. 2058 (Seifter) at 545, 546). This first step is required for the production of all classes of steroids produced in the adrenal gland or testes.

34. Figure 2 also shows the enzyme Cytochrome P450 17 α-hydroxylase/17,20-lyase ("CYP17"), which is a single protein that catalyzes two distinct activities, 17α-hydroxylase and 17,20-lyase. CYP17's 17α-hydroxylase activity converts (i) pregnenolone →17α-hydroxy pregnenolone and (ii) progesterone → 17α-hydroxy progesterone. CYP17's 17,20 lyase activity converts 17α-hydroxy pregnenolone → DHEA and (ii) 17α-hydroxy progesterone → androstenedione. (*See, e.g.*, Ex. 2086 (Princip. Endocr. Ch. 72) at 707).

35. Aldosterone is the primary mineralocorticoid in humans. (Ex. 2086 (Princip. Endocr. Ch. 72) at 710). Aldosterone is produced from pregnenolone via

the following pathway: pregnenolone → progesterone → deoxycorticosterone → corticosterone → aldosterone.

36. Cortisol is the major glucocorticoid in humans. (Ex. 2086 (Princip. Endocr. Ch. 72) at 709). Cortisol is produced from pregnenolone and progesterone, via for example: (a) pregnenolone →17α-hydroxy pregnelenone → 17α-hydroxy progesterone → 11-deoxycortisol → cortisol; or (b) pregnenolone → progesterone →17α-hydroxy progesterone →11-deoxycortisol → cortisol.

37. Androgens are formed from pregnenolone and progesterone via, for example: (a) pregnenolone →17α -hydroxy pregnenolone → DHEA pathway; or (b) pregnenolone → progesterone → 17α-hydroxy-progesterone → androstenedione pathway. (As I explained above, DHEA and androstenedione are adrenal androgens which can be converted into testosterone in the prostate. (Ex. 2086 (Princip. Endocr. Ch. 72) at 710).

38. The declaration of Mylan's expert, Dr. Garnick, contains a diagram entitled "Major Pathways in Steroid Biosynthesis". (Ex. 1002 (Garnick Dec.) at ¶37). The steroid synthesis diagram set forth in ¶ 37 of Dr. Garnick's declaration contains significant omissions. For example, the diagram does not identify desmolase, the enzyme that converts cholesterol to pregenenolone, which is the first step of steroid synthesis. This first step is very important because

pregnelonone is the precursor for all steroid hormones. Production of all steroids is suppressed if desmolase activity is inhibited.

39. In addition, Dr. Garnick's diagram does not clearly describe the dual 17α-hydroxylase and 17,20-lyase activities of CYP17. This is another important omission because as of August 2006, abiraterone acetate was known to differentially affect CYP17's 17α-hydroxylase and 17,20-lyase activities: the prior art showed that abiraterone acetate is a more potent inhibitor of the 17,20-lyase activity than 17α-hydroxylase inhibitory activity. (*See, e.g.*, Ex. 1003 (O'Donnell) at 2322); Ex. 1005 (Barrie) at col. 22:60-66).

3. Clinical Disorders Associated with Under-Production or Over-Production of Steroids and Their Treatment

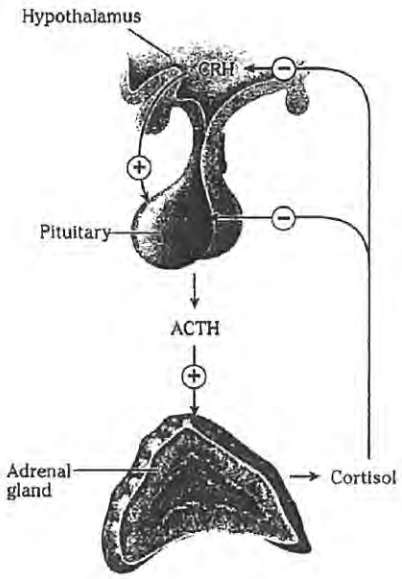
40. Levels of steroid hormones normally vary in response to changing conditions in the body. Interference with steroid synthesis can lead to clinical disorders that interfere with the body's normal response to stimuli. These disorders are classified as those that cause under-production or over-production of steroids. (Ex. 2058 (Seifter) at 545). Irregularities in steroid synthesis can occur due to many factors, for example, damage to the adrenal cortex, defects in the functioning of the hypothalamus or pituitary gland, or the actions of drugs that effect steroid hormone production.

41. Cortisol is the major glucocorticoid in humans. (Ex. 2086 (Princip. Endocr. Ch. 72) at 709). Cortisol has multiple functions in the body. The main

function of cortisol is to control cellular metabolism and glucose levels in the blood. Cortisol secretion is also necessary for the body to respond to stress (e.g., surgery, trauma, pain, infection, hypoglycemia, and hemorrhage). (*See, e.g.*, Ex. 2058 (Seifter) at 543-44).

42. Cortisol levels vary during the day, with peak values in the morning and low levels in the evening. (*Id.* at 548). The synthesis and secretion of cortisol is regulated by the central nervous system. In response to signals from the hypothalamus following neural stimuli, the anterior pituitary stimulates the release of adrenocorticotrophic hormone ("ACTH"). (*Id.* at 542.) ACTH acts on the adrenal cortex to increase synthesis of cortisol from cholesterol and its release by the adrenal cortex. As shown in Figure 3 below, cortisol production is tightly regulated to maintain its concentration in a physiologic range. This occurs not only through stimulation and secretion of cortisol by ACTH, but also through the negative feedback action of cortisol on the hypothalamus and pituitary to suppress secretion of ACTH. (*See generally* Ex. 2058 (Seifter) at 541-42; Ex. 2086 (Princip. Endocr. Ch. 72) at 710)).

Figure 3



43. The primary mineralocorticoid in humans is aldosterone. (Ex. 2086 (Princip. Endocr. Ch. 72) at 710). Aldosterone controls water and salt retention by increasing sodium reabsorption and potassium excretion. Aldosterone production is regulated not only by ACTH, but also by the renin-angiotensin-aldosterone system. (Ex. 2058 (Seifter) at 543)

44. Adrenal insufficiency is a clinical disorder that is typically characterized by the under-production of cortisol (a glucocorticoid) and aldosterone (a mineralocorticoid). Adrenal insufficiency can be "primary" (caused by impairment of the adrenal gland) or "secondary" (caused by impairment of the pituitary). (Ex. 2058 (Seifter) at 548-549).

45. Symptoms of primary adrenal insufficiency include, but are not limited to, severe fatigue, low blood pressure, low blood sugar, dizziness,

weakness, loss of appetite, weight loss, and increased skin pigmentation. (Ex. 2058 (Seifter) at 549; Ex. 1025 (Harrison's) at 2142).[3]

46. As of August 2006, treatment of adrenal insufficiency involved replacing or substituting the hormones (*i.e.*, glucocorticoids and mineralocorticoids) that the adrenal glands are not or are insufficiently making by administering physiologic or replacement doses of the under-produced hormones.

47. The most commonly employed hormone for glucocorticoid replacement therapy was hydrocortisone (the synthetic form of cortisol), which has both glucocorticoid and mineralocorticoid activity. (Ex. 1025 (Harrison's) at 2147). The synthetic glucocorticoid prednisone, which has slight to moderate mineralocorticoid activity, was also used for replacement therapy for patients with adrenal insufficiency. (*Id.*) The use of synthetic glucocorticoid dexamethasone, which has more potent glucocorticoid activity than hydrocortisone and prednisone is less common because it has less mineralocorticoid activity. (*Id.*)

48. Mineralocorticoid excess syndrome is a clinical disorder that is characterized by the excessive production of mineralocorticoids. (Ex. 2066 (Mantero) at 81; Ex. 2087 (Princip. Endocr. Ch. 73) at 717). Symptoms of

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[3] Deficiency of sex steroids is not a manifestation of adrenal insufficiency because they are produced predominantly by the gonads.

mineralocorticoid excess syndrome include hypertension (*i.e.*, high blood pressure), hypokalemia (*i.e.*, low potassium levels), and fluid retention. (Ex. 2066 (Mantero) at 82; Ex. 2087 (Princip. Endocr. Ch. 73) at 717). As of August 2006, it was known that symptoms of mineralocorticoid excess could be managed without glucocorticoid replacement, for example, by the use of drugs that block the activity of mineralocorticoids. (*See generally* Ex. 2066 (Mantero)). Indeed, this was the preferred method of treatment.

49. While certain treatments and disease states may be associated with changes in adrenal steroid levels, these changes may not be associated with clinical manifestations. Before glucocorticoid replacement is even considered, an essential first question that must be answered is whether the patient has a clinical disorder that is serious enough to warrant glucocorticoid replacement. This is because glucocorticoid therapy is not only associated with side effects and complications, but can also further reduce the body's ability to produce steroids. (I discuss these side effects and complications in detail *infra* in ¶¶ 131-142). This was well known as of August 2006, and remains true today. (*See, e.g.*, Ex. 2068 (Swartz) at 239 ("Before instituting corticosteroid therapy, it is necessary to carefully consider the gains that can be reasonably expected versus the potentially undesirable metabolic actions of large doses of corticosteroids. The increased incidence of hypertension, chronic infectious disease, osteoporosis and impaired glucose tolerance…must be

carefully considered before embarking on a programme of steroid administration"). Therefore, as of August 2006, a POSA would have been motivated to avoid administering glucocorticoid replacement therapy if a clinical condition could be managed without it.

50. Indeed, laboratory abnormalities showing over-production or under-production of steroid hormones in the absence of clinical manifestations were understood by a POSA to not require clinical intervention. In fact, laboratory evidence of corticosteroid deficiency in the absence of symptoms attributable to the deficiency would not have even been detected in routine clinical practice because the evaluation for corticosteroid deficiency would not be triggered in the absence of clinical symptoms. (Ex. 1025 (Harrison's) at 2142-43) (describing clinical signs and symptoms of adrenal insufficiency, which are to be confirmed by laboratory findings).

B. Prostate Cancer and Its Treatment as of August 2006

1. Prevalence, Diagnosis, and Early Stage Treatment

51. Globally, prostate cancer is the second most common cause of cancer other than non-melanomatous skin-cancer and the fifth leading cause of cancer-related death in men. Prostate cancer is also the second leading cause of cancer death in American men, behind only lung cancer. (Ex. 2027 (Rumohr) at 529; Ex. 2042 (Papatsoris) at 277). In the United States, 1 out of 7 men will be diagnosed

with prostate cancer, and approximately 1 out of 39 men will die of prostate cancer. (Ex. 2098 (ACS Statistics)). In 2017, in the United States, there are predicted to be 161,360 new cases of prostate cancer and 26,730 deaths. (Ex. 2098 (ACS Statistics).

52. Prostate cancer results from the uncontrolled growth of abnormal cells in the prostate gland. (Ex. 2091 (NIH Pamphlet) at 1). Androgens such as testosterone promote proliferation, growth, and survival of prostate cancer cells. (Ex. 2042 (Papatsoris) at 277; Ex. 2058 (Seifter) at 617). The most common sites of prostate cancer metastases (*i.e.*, spread of the cancer) are bone (approximately 90% of patients) and lymph nodes (approximately 40-50% of patients).

53. Patients with early stage prostate cancer can have few symptoms (and are often characterized as "asymptomatic"). When the disease is clinically "localized" (or has not yet spread), therapy often involves watchful waiting or "active surveillance." (Ex. 2091(NIH Pamphlet) at 13-14). For other patients, especially those with higher risk of progression and recurrence of their disease, treatment with surgery, radiation and/or hormone therapy can be applied. (*Id.* at 15-22). Approximately one third of all men who get treatment for localized prostate cancer have recurrence which eventually can progress to metastatic disease. (Ex. 1023 (Attard (2005)) at 1241).

2. First Line Hormonal Therapy for Metastatic Prostate Cancer

54. Since the 1940s, "androgen deprivation therapy" ("ADT") by surgical or medical castration has been the cornerstone of first line therapy for metastatic prostate cancer. (Ex. 1003 (O'Donnell) at 2317; Ex. 1023 (Attard (2005)) at 1241). ADT reduces testosterone to "castrate" levels. ADT can be accomplished by surgical or medical castration. (*Id.*). Surgical castration (also known as orchiectomy or orchidectomy) involves surgical removal of both testes, which directly removes the main source of testosterone, the principal androgen. (Ex. 1023 (Attard (2005)) at 1242). Medical castration involves the administration of drugs known as LHRH analogues, which interfere with testosterone production from the testes. (*Id.*) Irrespective of the method by which castration is achieved, androgen receptor antagonists (which competitively inhibit androgen binding to the androgen receptor) can be added.

3. Metastatic Castration Resistant Prostate Cancer

55. About 95% of men with metastatic prostate cancer respond initially to ADT. Ultimately, however, virtually all patients who receive ADT for prostate cancer manifest progression of the disease due to what was known as "resistance" to castration. The duration of response to ADT is highly variable with a median response of approximately 18-24 months.

56. Once patients manifest progression of their cancer on castration-based therapy, patients have what is now called metastatic "castration-resistant prostate cancer." ("mCRPC"). As of August 2006, the term "castration resistant prostate cancer" was not commonly employed. Instead, this state of resistance was termed "hormone-resistant prostate cancer," "hormone-refractory prostate cancer," or "androgen-independent prostate cancer." (Ex. 1001 ('438 Patent) at col. 16-17; Ex. 1004 (Gerber) at 1177; Ex. 1020 (Harris) at 542; Ex. 2042 (Papatsoris) at 271). Progression to mCRPC was associated with a poor prognosis with a median survival of approximately 12 months. (Ex. 1023 (Attard (2005)) at 1241).

57. As of August 2006, the mechanisms underlying the castration-resistant state were not fully understood and many operative factors and mechanisms were proposed, including mechanisms completely independent of androgens and/or the androgen receptor. (Ex. 2027 (Rumohr) at 529). In fact, the older terms for CRPC, namely "hormone resistant," "hormone-refractory," and "androgen-independent" all implied that further endocrine therapy would be ineffective.

58. While it was proposed that extra-testicular sources of androgens might activate the androgen receptor, as of August 2006, the role of the endocrine environment in mCRPC was not widely understood, and there was skepticism that further reduction of testosterone to "sub-castrate" levels or inhibition of adrenal

steroid production would benefit patients who were "castration resistant." (*See, e.g.*, Ex. 2028 (Judson Decl.) at ¶ 8; Ex. 2030 (CCR Letter) at 2). Nonetheless, it had been reported that intra-tumoral concentrations of androgens in mCRPC patients may be sufficient to activate the androgen receptor. (Ex. 1023 (Attard (2005)) at 1242). Importantly, no clinical trial had ever shown that secondary hormone therapies could improve the clinical outcomes of patients with mCRPC. Thus, the scientific literature did not establish any clinical evidence that secondary hormone therapies would be of clinical benefit to mCRPC patients.

59. Indeed, the issue of whether reduction of testosterone to sub-castrate levels would benefit patients was not resolved until the Phase III clinical studies with abiraterone acetate and prednisone, which provided definitive and proof-of-principle evidence that targeting the endocrine environment of mCRPC patients results in a clinical benefit.

60. As of August 2006, only limited success had been achieved with treatment of mCRPC. (Ex. 2027 (Rumohr) at 529). In 2004, two "landmark" Phase III clinical trials showed a modest survival benefit (approximately two months) of docetaxel chemotherapy in mCRPC patients, the first drug to do so. (Ex. 1022 (Tannock (2004); Ex. 2059 Petrylak (2006)). Docetaxel is a cytotoxic chemotherapy agent with a mechanism of action that is very different from hormone therapies. Despite this, many patients could not tolerate the severe

toxicities associated with cytotoxic chemotherapy, and others were ineligible for treatment. Other than docetaxel chemotherapy, the available treatments provided only short-term relief, and none of these treatments improved survival. (Ex. 1023 (Attard (2005)) at 1241; Ex. 2042 (Papatsoris) at 278).

61. Notwithstanding its limitations, the focus of additional clinical trials was on improving the survival benefit seen with docetaxel-based chemotherapy. (Ex. 2031 (Burgess & Roth) at *Abstract*, 227, 229-233; *see also* Ex. 1022 (Tannock (2004)). These efforts involved combining novel agents with docetaxel and developing new classes of cytotoxic agents, as well as new cytotoxic agents in known classes (Ex. 2032 (Strother) at 954-55; Ex. 2036 (Hadaschik) at 185). In addition, a wide range of alternative (*i.e.*, non-chemotherapy) strategies were also explored, including, but not limited to, angiogenesis inhibitors, targeted agents, agents that target specific biochemical pathways, and bone targeting agents. (Ex. 2042 (Papatsoris) at 278-80). In fact, as of 2006, "[o]ver 200 compounds ha[d] entered clinical development for use in advanced prostate cancer." (Ex. 2043 (Armstrong) at 138). To the extent they were considered, disparate classes of secondary hormonal agents were also investigated with little success, including androgen receptor targeting agents and estrogenic compounds.

C. Endpoints for Evaluating Response to Prostate Cancer Treatment

62. Until the mid-1990s, the primary method for monitoring the progression of prostate cancer and associated metastases was through radiologic procedures and imaging, which permitted visualization of the tumor, and its progression, within the body. In 2000, the Response Evaluation Criteria in Solid Tumors Group (RECIST) published a standardized set of criteria for the measurement and assessment of tumor lesions with the goal of ensuring more uniform reporting of outcomes of clinical trials. (Ex. 2046 (Therasse)). These guidelines were adopted by researchers and clinicians as an "objective tumor response" to evaluate therapeutic strategies for prostate cancer. As of August 2006, objective tumor responses were widely used in clinical practice (for making decisions about continuation of current therapy), and in clinical trials (as a surrogate endpoint for other measures of clinical benefit such as overall survival).

63. As of August 2006, "subjective" assessments, such as pain, palliation, and quality of life, which relied upon patient-reported outcomes, were sometimes included as endpoints in clinical trials of prostate cancer therapies; however, it was known that such subjective endpoints did not necessarily reflect changes in the size or extent of prostate cancer tumors. Although standardized questionnaires were being developed to assess such subjective endpoints, these were known to have

shortcomings that limited their usefulness. For therapies developed to elicit an anti-tumor response, the standard endpoint was survival.

64. In the late 1970s, the glycoprotein prostate-specific antigen ("PSA") was isolated and found to be present almost exclusively in normal and neoplastic prostate cells and seminal fluids. In 1987, the New England Journal of Medicine published a study examining the potential use of PSA as a biomarker for prostate cancer, which suggested that PSA could be useful in monitoring patient response to prostate cancer therapy. (Ex. 2047 (Stamey) at *Abstract*). Following the publication of Stamey, researchers began to measure serum PSA levels in patients with prostate cancer with the hope of reliably demonstrating that changes in PSA levels could be useful as an indicator of disease regression or progression and response to treatment. In 1999, following a consensus conference, the Prostate-Specific Antigen Working Group ("PSA Working Group"), a group of 26 leading clinical researchers published eligibility and response guidelines for clinical trials in androgen-independent prostate cancer, explaining that "it was important for investigators to agree on definitions and values for a minimum set of parameters for eligibility and PSA declines and to develop a common approach to outcome analysis and reporting" in clinical trials. (Ex. 2057 (Bubley) at 3461).

65. The PSA Working Group researchers recognized that "some of the data currently available suggests that serum PSA cannot serve as a reliable

surrogate end point because "there is no consistency in how a PSA decline is measured and reported." (*Id.* at 3462). Nevertheless, the Working Group also noted that "many but not all investigators have observed an association between a decline in PSA levels of 50% or greater and survival." (*Id.* at 3461).

66. Therefore, the researchers proposed that to use PSA effectively, investigators agree on a set of criteria for PSA response. (*Id.*). The guidelines proposed that investigators define a "PSA response" as, at a minimum, a PSA decline of at least 50% confirmed by a second PSA value 4 or more weeks later. (*Id.* Abstract): "[I]nvestigators should report, at minimum, a PSA decline of at least 50%, which must be confirmed by a second PSA value 4 or more weeks later. The reference PSA for these declines should be a PSA measured within 2 weeks before starting therapy. Patients may not demonstrate clinical or radiographic evidence of disease progression during this time period." (*Id.* at 3464). The goal of the proposed guidelines was "to use [PSA] as an outcome measure to guide the development of further trials, generally randomized." (*Id.*).

67. By 2006, these guidelines were widely applied by researchers and clinicians for evaluating response to therapeutic agents in mCRPC patients. Accordingly, researchers and clinicians who used PSA as a measurement of outcome understood that, as a threshold standard, patients who showed a greater

than 50% decrease in PSA were likely to have actually experienced a clinically significant response.

68. While both PSA measurement and imaging procedures were considered useful as surrogate endpoints in prostate cancer treatment evaluation, as of August 2006, the gold standard for evaluating quantitative impact on life expectancy for any anti-cancer treatment was survival.

IV. THE '438 PATENT AND ITS CLAIMS

69. The '438 patent, entitled "Methods and Compositions for Treating Cancer," was issued on September 2, 2014. (Ex. 1001 ('438 Patent)).[4]

70. The '438 patent contains 20 claims. Claim 1, the only independent, recites:

> A method for the treatment of a prostate cancer in a human comprising administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of prednisone. (*Id.* at col. 16).

71. Claims 2 to 20 depend from claim 1 and set forth additional limitations of the claimed treatment method, including the amount of abiraterone

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[4] I understand that the '438 patent issued from Application No. 13/034,340, filed on February 24, 2011, which is a continuation of application No. 11/844,440, filed on August 24, 2007, now abandoned, which claims priority to Provisional Application No. 60/921,506, filed on August 25, 2006. (*Id.*).

acetate and the amount of prednisone used in the claimed methods, and the type of prostate cancer being treated. (*Id.* at col. 16-17). The text of Claims 2-20 is set forth below:

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

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

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

Claim 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.

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

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

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

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

Claim 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.

Claim 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.

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

Claim 13. The method of claim **12**, wherein the refractory prostate cancer is not responding to at least one anti-cancer agent.

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

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

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

Claim 17. The method of claim **14**, wherein the anti-neoplastic agent comprises docetaxel.

Claim 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.

Claim 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.

Claim 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.

72. The '438 patent explains that abiraterone acetate is a specific inhibitor of the dual-functioning enzyme known as CYP17. CYP17 activity is required for androgen synthesis by the body, including synthesis of testosterone. (*Id.* at Col. 3:66 to Col. 4:1).

V. CLAIM CONSTRUCTION

73. I understand that the Panel has construed certain terms that are used in the '438 Patent. I have read and understood the Panel's claim constructions and my opinions set forth herein apply these meanings.

74. The Panel has construed "anti-cancer agent" as "any therapeutic agent that directly or indirectly kills cancel cells or directly or indirectly prohibits, stops, or reduces the proliferation of cancer cells."

75. The Panel has construed "refractory cancer" as "cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment."

76. The Panel has construed "therapeutically effective amount of prednisone" as "an amount of prednisone effective for treating prostate cancer."

77. The Panel has construed "treat," "treating," and "treatment," to mean "include the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer." Each of these effects pertains to reducing the growth or spread of the cancer itself.

VI. PERSON OF ORDINARY SKILL IN THE ART

78. In my opinion, a POSA with respect to the '438 Patent is a physician specializing in urology or medical oncology who has significant practical

experience in the treatment of patients with prostate cancer. Such a person would have worked in a team or setting that includes access to one or more individuals who have expertise in endocrinology, biochemistry, pharmacology, and/or molecular biology or a related field of science, and who has experience in prostate cancer treatments or androgen synthesis and action.

79. I have reviewed the definition of a POSA set forth in the declaration of Petitioner's expert, Dr. Garnick. (Ex. 1002 (Garnick Dec.) at ¶¶ 18-20). Petitioner's POSA definition embraces too wide a range of skills to have any use or meaning in addressing the validity issues in the Petition. Nevertheless, even under Petitioners' definition of a POSA, my opinions set forth herein would remain unchanged.

VII. THE PRIOR ART RELIED ON BY PETITIONERS

A. Gerber (Exhibit 1004)

80. Petitioners rely upon Gerber *et al.*, Prostate Specific Antigen for Assessing Response to Ketoconazole and Prednisone in Patients with Hormone Refractory Metastatic Prostate Cancer, *J. Urology*, 144(5):1177-9 (1990) ("Gerber") (Exhibit 1004). Gerber is a retrospective chart review of serial PSA levels in 15 men with hormone refractory (*i.e.*, castration-resistant) metastatic prostate cancer who were administered ketoconazole and prednisone. (*Id.* at *Abstract*).

81. Gerber explains that ketoconazole was originally developed as an antifungal agent. (*Id.* at 1177). Gerber also explains that it had been observed that ketoconazole is a potent inhibitor of gonadal and adrenocortical steroid synthesis and had an *in vitro* cytotoxic effect on prostate cancer cells, findings which suggested a potential role for ketoconazole in prostate cancer. (*Id.*)

82. Gerber also cites to reports from the late 1980s in which mCRPC patients were given ketoconazole (alone or in combination with prednisone) as an option of last resort. Gerber states, however, that results from studies evaluating the use of ketoconazole for the treatment of mCRPC "have not been . . . promising." (*Id.* at 1177). Gerber states that in the earlier reports, ketoconazole either had "limited use" or resulted in overall PSA changes that "did not reliably reflect disease response or progression." (*Id.* at 1179).

83. The stated aim of Gerber was to assess whether serial PSA levels in men with mCRPC administered ketoconazole and prednisone could be used as a possible surrogate for disease progression and regression. (*Id.* at 1177, 1179). Patients were administered 600 to 900 mg of ketoconazole daily in 3 divided doses and 5 mg of prednisone twice per day; ketoconazole dosage was increased to 1,200 mg daily if the PSA level did not decrease. (*Id.* at 1178).

84. Gerber could not assess whether the combination of prednisone and ketoconazole was safe and effective for the treatment of prostate cancer because it

was not a formal study designed to assess those outcomes, which would need to be properly evaluated using a well-controlled randomized clinical trial.

85. Gerber reports that of the 15 patients given ketoconazole and prednisone, 12 (80%) had a decrease in PSA with a median duration of response of 3 months. (*Id.* at *Abstract*, 1178). In 9 of 12 men, the improvement in PSA was "short-lived (*i.e.* less than or equal to four months)") and "occasionally of small magnitude." (*Id.* at 1179). Gerber concludes that "[s]hort-term decreases in PSA are of unclear importance but probably do not reflect significant disease regression" and "it is unlikely that significant impact on survival will be seen in these cases." (*Id.*).

86. Gerber also states that 3 of 15 patients (20%) had a "prolonged response of 8 to 10 months (see table)." (*Id.* at 1178-79). The cited table shows that, of the three patients, 1 had a PSA decline of 40% (second course of therapy after initial progression) and 2 patients had PSA declines greater than 50%. (*Id.* at 1178).

87. Gerber does not specify the minimum change in PSA level that was to be considered a "response" to ketoconazole and prednisone. Rather, Gerber includes as "responders" any patient who experienced any measurable decline in PSA. (*See, e.g., id.* at 1178, in which one "'responding patient[]'... had a 7% decrease in PSA").

88. Gerber cites to studies in which ketoconazole was administered as a monotherapy without glucocorticoid replacement. (*Id.* at 1177) (citing Williams *et al.*, (1986) (Ex. 2020).

B. The Barrie patent (Exhibit 1005)

89. U.S. Patent No. 5,604,213 to Barrie *et al.* (the "Barrie patent") (Ex. 1005) was filed on September 30, 1994 and issued on February 18, 1997.

90. The Barrie patent describes and claims 17-substituted steroid compounds that are inhibitors of "[t]he 17α-hydroxylase/ $C_{17, 20}$-lyase enzyme complex." (*Id.* at cols. 1, 17-18, 27-30). Abiraterone acetate is just one of numerous compounds disclosed. (*Id.* at col. 2: 56 to col. 5:34). The Barrie patent does not contain any clinical data relating to abiraterone acetate administration.

91. The Barrie patent discloses *in vivo* test results in mice measuring the effects of abiraterone acetate and ketoconazole on organ weight (such as adrenal, prostate, seminal vesicle, and testes) and hormone levels (testosterone and luteinizing hormone). The data show that the reduction in weight of the prostate, seminal vesicles, and testes were greater for abiraterone acetate than ketoconazole. These results would have confirmed to a POSA that abiraterone acetate more selectively and effectively inhibited testosterone synthesis compared to ketoconazole. (*Id.* at col. 25:13 to col. 26:64, Table 3, 4).

C. O'Donnell (Exhibit 1003)

92. Petitioners also rely on O'Donnell *et al.*, "Hormonal impact of the 17α-hydroxylase/C17,20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer," *British J. Cancer*, 90:2317-2325 (2004) ("O'Donnell") (Ex. 1003) was published in May 2004.

93. O'Donnell describes the results of three separate Phase I (safety and toxicity) studies conducted to determine the dose of abiraterone acetate that would result in maximum suppression of testosterone synthesis in castrate and non-castrate patients with prostate cancer. (*Id.* at *Abstract*, 2317, 2318-19). Endocrine data was also collected to determine the specificity of abiraterone acetate's enzyme inhibition. (*Id.*)

94. O'Donnell describes three separate clinical trials: (1) Study A (a single dose trial in males with castrate levels of testosterone following surgical or medical castration); (2) Study B (a single dose study in non-castrate males); and (3) Study C (a multi-dose study in non-castrate males). (*Id.* at 2318-19; 2320-22; Figs. 3-5). O'Donnell teaches that in each study abiraterone acetate was administered as monotherapy (*i.e.*, without corticoisteroids). (*Id.* at 2319) ("patients were not allowed to take concomitant steroids").

95. The results reported in O'Donnell showed that abiraterone acetate treatment reduced testosterone levels in both castrate and non-castrate patients with

prostate cancer administered single and multiple doses of 500 mg-800 mg abiraterone acetate. (*Id.* at *Abstract*, 2320-22). However, none of the studies measured the effects of abiraterone acetate on PSA or any objective tumor response criteria. (*Id.* at 2318-20). As safety studies, the clinical trials reported in O'Donnell were not designed to examine, and did not establish, clinical efficacy of abiraterone acetate. Indeed, contemporaneous references viewed the results in O'Donnell as not showing any evidence of clinical efficacy. (Ex. 1023 (Attard (2005) at 1245) ("while the [O'Donnell] data are encouraging … there is no evidence of clinical efficacy")).

VIII. Rebuttal to Dr. Garnick's Opinions Concerning Obviousness

96. I understand that Mylan's expert, Dr. Garnick, states in his declaration that Claim 1-20 of the '438 patent are unpatentable as obvious over (a) O'Donnell in view of Gerber; or (b) the Barrie patent in view of Gerber. (Ex. 1002 (Garnick Decl.) at ¶¶ 54-76). I disagree. Dr. Garnick's declaration, which I have reviewed, contains a number of fundamental scientific errors concerning the teachings of the prior art. When the scientifically correct teachings of the prior art as a whole are considered, the claims of the '438 patent are not obvious.

A. There Was No Scientific Basis in the Prior Art to Add Prednisone to Abiraterone Acetate for Purposes of Glucocorticoid Replacement

1. As of August 2006, a POSA Would Understand that Abiraterone Acetate's Mechanism of Action and Hormonal Side Effects Were Very Different from Ketoconazole

97. Dr. Garnick mischaracterizes abiraterone acetate and ketoconazole as similar "CYP17 inhibitors," suggesting that both compounds reduced androgen levels by the same mechanism of action, and had similar hormonal side effects. (*See, e.g.*, Ex. 1002 (Garnick Decl.) at ¶¶ 33, 36-37, 40-41, 43-44, 54, 58-59). Dr. Garnick's opinions are scientifically incorrect and have no support in the prior art. Indeed, both O'Donnell and the Barrie patent teach that abiraterone acetate's mechanism of action for reducing androgens is very different from ketoconazole. In addition, as the schematics in Figure 4 and Figure 5 illustrate, abiraterone acetate's specific inhibition of the CYP17 enzyme is very different from ketoconazole's nonspecific inhibition of multiple enzymes in the adrenal steroid synthesis pathway, and as a result, the biochemical and clinical effects of one cannot be ascribed to the other.

Figure 4: Abiraterone Acetate - Selective Inhibition

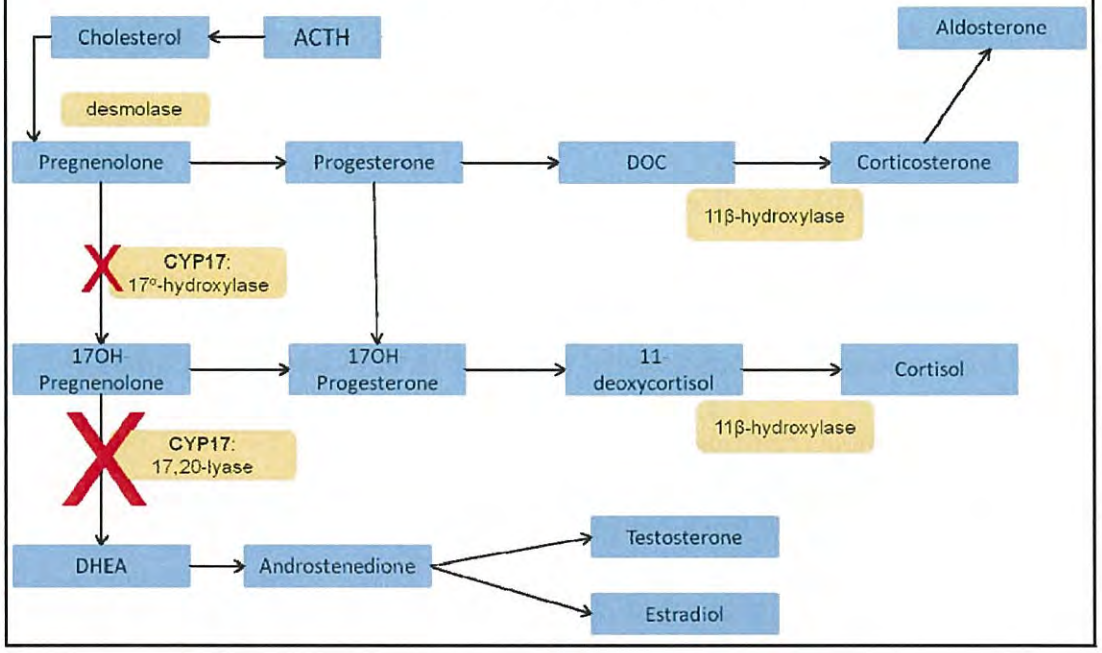
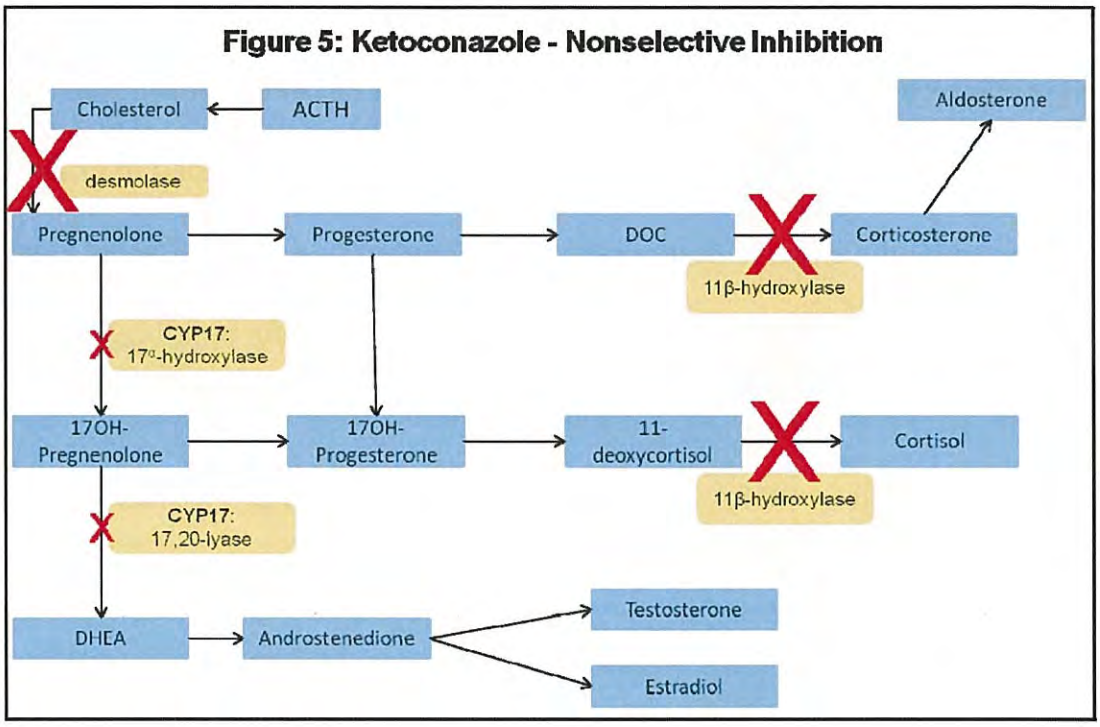


Figure 5: Ketoconazole - Nonselective Inhibition



98. O'Donnell teaches that "[t]he novel 17α-hydroxylase/$C_{17,20}$-lyase inhibitor abiraterone acetate ...was developed as a mechanism-based steroidal

inhibitor following observations that nonsteroidal 3-pyridyl esters had improved selectivity for inhibition [of CYP17]." (Ex. 1003 (O'Donnell) at 2318) (emphasis added). O'Donnell also teaches that "[t]his is the first report of the effects of a specific 17α-hydroxylase/$C_{17,20}$-lyase inhibitor in humans." (*Id.*) (emphasis added). A POSA would understand from these teachings concerning specificity that abiraterone acetate targets only CYP17 and does not inhibit other enzymes in the steroid synthesis pathway. (*Id.* at 2318 Figure 1).

99. O'Donnell does not indicate that ketoconazole inhibits the CYP17 enzyme or that ketoconazole is a "CYP17 inhibitor." To the contrary, O'Donnell teaches that "[k]etoconazole is relatively unselective, inhibiting both cholesterol side chain cleavage and 11β-hydroxylase." (*Id.* at 2318) (emphasis added).

100. The "cholesterol side chain cleavage" step described in O'Donnell is catalyzed by the enzyme desmolase and is the very first step in steroid synthesis, during which cholesterol is converted to pregnenolone, the building block for all steroid hormones. (*Id.* at 2318 Figure 1). Inhibition of this first step would have been understood by POSA to suppress the production of all steroids downstream of cholesterol. (*Id.*)

101. Thus, a POSA would understand from O'Donnell that, unlike abiraterone acetate, which has a mechanism of action selective for CYP17, ketoconazole acts as a blunt instrument that inhibits androgen production by

inhibiting all adrenal steroid synthetic pathways, including glucocorticoids and mineralocorticoids. (*Id.*)

102. Additional prior art also teaches that "[k]etoconazole ... suppresses testicular and adrenal steroidogenesis by inhibition of the conversion of cholesterol to pregnenolone [*i.e.*, the first steroid synthesis step]...ketoconazole is a potent inhibitor of all adrenal steroid synthetic pathways." (Ex. 1020 (Harris) at 544 (emphasis added); *see also* Ex. 1004 (Gerber) at 1177 ("[ketoconazole] is a potent inhibitor of gonadal and adrenocortical steroid synthesis") (emphasis added)).

103. The Barrie patent confirms that abiraterone acetate and ketoconazole reduce androgens by very different mechanisms. As discussed, the Barrie patent teaches that, in mice, "[k]etoconazole caused an increase in adrenal weight at the two highest doses, whereas [abiraterone acetate] had no significant effect, suggesting that [it] did not inhibit corticosterone biosynthesis." (Ex. 1005 at col. 25:45-49). I understand from the declaration of Patent Owner's expert, Dr. Richard Auchus, that as of August 2006, a POSA would understand that the increase in adrenal weight caused by ketoconazole signified an accumulation of cholesterol in the adrenal glands, which, in normal rodents, is converted to various adrenal steroids through the steroid synthesis pathway. (Ex. 2040 (Auchus Decl.) at ¶ 44). This is consistent with ketoconazole's blunt mechanism of action, which

inhibited the production of all adrenal steroids because of ketoconazole's inhibition of desmolase (the first step of the steroid synthesis pathway). (*Id.*).

104. In contrast, I understand from Dr. Auchus's declaration that the fact Barrie teaches that abiraterone acetate had "no significant effect" on adrenal weight would have confirmed to a POSA that abiraterone acetate acted via a more selective and different mechanism than ketoconazole. (*Id.* at ¶ 45). In particular, Dr. Auchus explains that a POSA would conclude from this teaching in the Barrie patent that while ketoconazole inhibited conversion of cholesterol to steroid precursors, abiraterone acetate allowed such conversion, such that it had "no significant effect" on adrenal weight compared to ketoconazole. (*Id.*).

105. Further, I understand from Dr. Auchus that corticosterone is the primary glucocorticoid in rodents. (*Id.* at ¶ 46). Therefore, I understand from Dr. Auchus's declaration that a POSA would understand from the Barrie patent that in a mammal receiving abiraterone acetate, glucocorticoids could continue to be made because the Barrie patent teaches that abiraterone acetate "did not inhibit corticosterone biosynthesis." (*Id.* at ¶¶ 43, 45).

106. As of August 2006, a POSA would understand that as a result of their different mechanisms of action, abiraterone acetate and ketoconazole would cause different hormonal side effects in patients. As of August 2006, there was clinical evidence that showed that ketoconazole's suppression of all adrenal steroid

synthesis resulted in the under-production of both glucocorticoids and mineralocorticoids, causing clinical symptoms of adrenal insufficiency. (Ex. 2090 (Tucker) at 2413-14; Ex. 2018 (Jubelirer) at 90). Glucocorticoid (and mineralocorticoid) replacement was given with ketoconazole for purposes of treating adrenal insufficiency. (Ex. 1025 (Harrison's) at 2144 (explaining that adrenal insufficiency occurred with ketoconazole); *see also* Ex. 1020 (Harris) at 544 (explaining that replacement doses of hydrocortisone may be required "[b]ecause ketoconazole is a potent inhibitor of all adrenal steroid synthetic pathways") (emphasis added)).

107. But as explained above, as of August 2006, a POSA would understand from O'Donnell and the Barrie patent that because of its specific mechanism of action, unlike ketoconazole, abiraterone acetate did not suppress all adrenal steroid synthesis pathways. To the contrary, POSA would understand that abiraterone acetate administration would still allow for the production of other adrenal steroids that the body needs, such as glucocorticoids and mineralocorticoid (*see* Ex. 1003 (O'Donnell) at 2318 Figure 1; *see also infra next section* discussing cortisol production by abiraterone acetate).

108. The central premise of Dr. Garnick's opinions is that clinical experience with ketoconazole would have been translated to abiraterone acetate because both compounds acted the same. But this is not true and a POSA would

not have viewed this to be the case. Indeed, as discussed more fully below, O'Donnell does not teach or suggest that abiraterone acetate caused any clinical symptoms of under-production of glucocorticoids such as those known to occur with ketoconazole.

2. As of August 2006, a POSA Would Understand that Abiraterone Acetate Did Not Cause Clinical Symptoms Associated with Adrenal Suppression and Maintained Normal Cortisol Levels

a. O'Donnell teaches that abiraterone acetate did not have any significant effect upon cortisol levels in patients

109. As of August 2006, a POSA would understand that the different mechanisms of action between ketoconazole and abiraterone acetate resulted in different clinical effects. In particular, a POSA would understand from O'Donnell that, unlike ketoconazole, abiraterone acetate did not cause any clinical symptoms necessitating glucocorticoid replacement. In my opinion, this understanding completely undermines Dr. Garnick's theory of obviousness because it rests almost entirely on so-called "safety and tolerability" issues associated with abiraterone acetate. In fact, no "safety and tolerability" issues of any significance were reported in the literature. In the absence of any such clinical issues, a POSA had many compelling reasons to *avoid* using glucocorticoids.

110. Under "Overall Toxicity," O'Donnell states that "[i]n all three trials, abiraterone acetate was very well tolerated and no serious adverse events

attributable to treatment were recorded. No haematologic or biochemical effects were observed at any dose level or schedule evaluated. No alteration in resting heart rate or blood pressure was seen." (Ex. 1003 (O'Donnell) at 2322) (emphasis added). These statements are significant because O'Donnell was primarily designed to study the safety and toxicity of abiraterone acetate.

111. Further, under "Results" and in the "Discussion" section, O'Donnell teaches that for each of Study A, Study B, and Study C, there was no significant effect on serum cortisol levels. In fact, O'Donnell indicates that these did not change significantly and remained within normal limits. (*Id.* at 2320-22). Thus, a POSA would have found no clinical evidence in O'Donnell that would have suggested a need for glucocorticoid replacement therapy.

112. The results of Study A in O'Donnell show that abiraterone acetate did not have any significant effect on cortisol levels in patients. Discussing Study A, O'Donnell states that:

> This single dose study showed no effect on 17α-OH-progesterone production. This indicates that any inhibition of 17-α-hydroxylation that may occur as a result of treatment with abiraterone acetate is overridden by compensatory mechanisms related to cholesterol feedback. Despite 17-α-hydroxylase and C17,20-lyase activities being contained in a single enzyme, the compensated effect on 17-α-hydroxylase activity clearly did not prevent an inhibition of C17,20-lyase (as evidenced by androgen suppression). Supportive evidence for this is provided by the observation that there

> was no significant effect on cortisol levels in these patients.

(*Id.* at 2322-23) (emphasis added). Further, O'Donnell states that "[a] reduction in serum cortisol levels was seen in one patient treated at 500 mg …[h]owever, as this reduction was apparent at the first time point on Day 1 it was felt to be inconsistent with suppression due to abiraterone." (*Id.* at 2320).

113. As I have explained above, production of 17α-hydroxy progesterone requires 17α-hydroxylase activity, and is an intermediate in the pathway for cortisol production. (*See supra* at ¶¶ 27, 34-36). Therefore, a POSA would understand from the above passages in O'Donnell describing Study A that administration of abiraterone acetate inhibited androgens by inhibiting 17,20-lyase but allowed CYP17's 17α-hydroxylation activity, and that, because of this, it did not have a clinically significant effect on cortisol levels.

114. The other O'Donnell studies also confirmed that abiraterone acetate did not have a clinically significant effect on cortisol levels. With respect to Study B, O'Donnell states that "[n]o change in cortisol level was seen." (Ex. 1003 (O'Donnell) at 2321). Discussing Study C, O'Donnell also states that "serum cortisol levels remained within normal limits." (*Id.* at 2321).

115. O'Donnell states that in Study C, "three patients treated at the 500 mg level had an abnormal response to the Synacthen test by Day 11," which result was also seen in three patients treated at 800 mg. (*Id.* at 2321). Further, O'Donnell

states that "[a]lthough baseline cortisol levels remained normal, all patients treated at 500 and 800 mg in the multiple dose study [C] developed an abnormal response to a short Synacthen test by Day 11. Some impact on adrenal reserve was predictable from the steroid synthesis pathway." (*Id.* at 2323). Further, although serum cortisol levels were reduced by evening on Day 1 in three patients who received 800 mg, "all other assessments remained within normal limits." (*Id.* at 2321).

116. Importantly, in my opinion, a POSA would have not considered the teaching in O'Donnell of "abnormal" Synacthen test results in isolation. Rather, a POSA would have considered the teachings of O'Donnell as a whole, including the teaching that abiraterone acetate was "very well tolerated and no serious adverse events attributable to treatment were recorded," and that "cortisol levels remained normal." (Ex. 1003 (O'Donnell) at 2322, 2323).

117. Further, I understand from Dr. Auchus's declaration that the Synacthen test is a laboratory test used to evaluate adrenal function in patients, specifically, the ability of the adrenal gland to respond to a stress stimulus. (Ex. 2040 (Auchus Decl.) at ¶ 13). I further understand that as of August 2006, Synacthen test results were typically reported as a "pass"/ "fail" or "positive"/"negative" for each individual patient, generally approximately 500 nmol/L. In addition, I understand that it was known that Synacthen test results

reported as an absolute or percentage change from a baseline level were not useful. (*Id.* at ¶¶ 14, 15). Because the data was not reported correctly, I understand that a POSA would have considered the Synacthen test results reported in O'Donnell to be inconclusive in determining if a patient had diagnosable adrenal insufficiency. (*Id.* at ¶ 32).

118. I further understand from Dr. Auchus's declaration the Synacthen test only measures a patient's cortisol levels in response to stress, but does not measure the total amount of glucocorticoids being produced by the patient. For example, the Synacthen test reported in O'Donnell does not measure the level of corticosterone, which has glucocorticoid activity. (*Id.* at ¶ 33). Therefore, I understand that the Synacthen test results in O'Donnell do not account for all the glucocorticoids being made in the body, and the reported Synacthen test result could be below a threshold value for cortisol without there being a clinical glucocorticoid deficiency. As I have explained, a physician would not administer glucocorticoid replacement based solely upon the results of a Synacthen test only measuring cortisol, but instead would do a full work up of the patient, with a focus on their clinical symptoms.

119. Indeed, in light of the known significant toxicities of glucocorticoids (*see infra* at ¶¶ 131-142), a POSA would have avoided co-administering glucocorticoids unless clinical evidence (*i.e.*, symptoms) showed that it was

necessary to do so. But a POSA would have found no clinical evidence in O'Donnell that would have suggested a clinical need for glucocorticoid replacement therapy.

120. The Barrie patent adds nothing to the teachings of O'Donnell. The Barrie patent contains no clinical data and does not mention glucocorticoid replacement. (Ex. 1005 (Barrie)). In addition, as explained above, I understand from Dr. Auchus's declaration that a POSA would understand from the Barrie patent that following abiraterone acetate administration to a mammal, glucocorticoids continued to be made. (Ex. 2040 (Auchus Decl.) at ¶¶ 43, 45 47).

b. A POSA Would Have Concluded from the Prior Art as a Whole that Abiraterone Acetate did not Cause Any Clinical Symptoms Requiring Glucocorticoid Replacement

121. O'Donnell states that:

> Adrenocortical suppression may necessitate concomitant administration of replacement glucocorticoid ...
>
> In the clinical use of both aminoglutethimide and ketoconazole, it is common practice to administer supplementary hydrocortisone and this may prove necessary with 17α-hydroxylase and $C_{17, 20}$-lyase inhibitors such as abiraterone acetate. However, the omission of glucocorticoid replacement when treating with aminoglutethimide and ketoconazole has been shown to be safe and effective. [Citations omitted]. In the light of this clinical evidence, further studies with abiraterone acetate will be required to ascertain if concomitant therapy with glucocorticoid is required on a continuous basis, at times of physiological stress, if

patients become symptomatic, or indeed at all." (*Id.* at *Abstract*, 2323) (emphasis added).

122. As of August 2006, a POSA would understand that the above statements in O'Donnell were speculative and would not have considered them in isolation, but rather in light of the clinical evidence. That clinical evidence showed that "abiraterone acetate was very well tolerated and no serious adverse events attributable to treatment were recorded. No haematologic or biochemical effects were observed at any dose level or schedule evaluated. No alteration in resting heart rate or blood pressure was seen." (*Id.* at 2322). Indeed, other prior art references interpreting the results reported in O'Donnell confirmed that abiraterone acetate does not cause clinical symptoms associated with adrenal insufficiency that would require glucocorticoid replacement. (*See, e.g.,* Ex. 1023 (Attard (2005)) at 1245 (stating concerning the O'Donnell studies that "there were no clinical manifestations of adrenocortical insufficiency"); Ex. 1080 (Lam) at 30 (stating that "abiraterone acetate is well tolerated…no serious side effects have been reported.").

123. Therefore, if anything, the statement that the "omission of glucocorticoid replacement when treating with aminoglutethimide and ketoconazole has been shown to be safe and effective" would have led a POSA to question whether glucocorticoid replacement was even necessary for ketoconazole, which unselectively inhibits several enzymes in the adrenal steroid synthesis

pathway, let alone for the specific CYP17 inhibitor, abiraterone acetate. (Ex. 1003 (O'Donnell) at 2323).

124. Indeed, a POSA would have considered all of the teachings in O'Donnell as a whole, as well as additional teachings in the prior art that taught that glucocorticoid replacement should only be given if there was a clear clinical need. From the perspective of the prior art as a whole, a POSA would understand that, because no symptoms suggesting a serious glucocorticoid deficiency were observed and because cortisol levels remained normal following abiraterone acetate administration, the results reported in O'Donnell, the only clinical studies of abiraterone acetate available at the time of the invention, showed there was no clinical need for glucocorticoid replacement.

125. O'Donnell, after noting that ketoconazole is often "safe and effective" *without* co-administration of glucocorticoids, indicates that "further studies" were needed before any conclusions could be reached concerning whether to give glucocorticoid therapy "on a continuous basis" or "at times of physiological stress," or "indeed at all" with abiraterone acetate. A POSA would understand that if the authors were suggesting that glucocorticoid co-administration with abiraterone acetate was warranted, they would not have made reference to the fact that ketoconazole can be safely administered without glucocorticoid replacement therapy.

126. O'Donnell teaches a POSA to not blindly administer a glucocorticoid with abiraterone acetate without clinical evidence demonstrating a need for glucocorticoid replacement. A POSA would be particularly reluctant to administer glucocorticoid replacement therapy absent clinical evidence demonstrating such a need due to the many known serious side effects of glucocorticoids. A POSA would understand O'Donnell to be inconclusive regarding whether glucocorticoid replacement would be required at all, on a continuous basis or only "during times of physiological stress," at which time abiraterone acetate would possibly be discontinued. During times of physiologic stress such as, for example, surgery or severe infection, there would be no urgent need to continue taking abiraterone acetate. It would be reasonable to hold administration of abiraterone acetate during the acute stress episode, administer any necessary stress doses of glucocorticoid until the physiologic stress subsided, and then reintroduce the abiraterone acetate when stress doses of glucocorticoid were no longer needed.

127. O'Donnell concludes by proposing that the next study of abiraterone acetate should be a "chronic dosing Phase I/II study in GnRH [castrate] resistant prostate cancer in the presence of continued GnRH dosing." Ex. 1003 at 2324. Notably, while O'Donnell specifies that abiraterone acetate should be tested in combination with continued GnRH dosing, O'Donnell does not make any mention of co-administering abiraterone acetate with a glucocorticoid in the proposed

follow-up study. A POSA would understand the authors' proposed study, which does not include concomitant glucocorticoid administration, to further reinforce that abiraterone acetate did not require co-administration of a glucocorticoid.

128. It is my understanding that, in fact, the next clinical studies with abiraterone acetate were both Phase I/II studies in which abiraterone acetate was administered as a monotherapy to patients with mCRPC. (Ex. 2014 (Attard 2008) at 4563, 4565; Ex. 2133 (Ryan 2010) at 1481, 1482). The COU-AA-001 and COU-AA-002 studies were designed and took place in the UK and US, respectively, after the publication of O'Donnell manuscript and prior to August 2006. (*Id.*). This is real-world evidence confirming that a POSA faced with the teachings of O'Donnell prior to August 2006 would have understood abiraterone acetate to be safe for administration as a single agent and would not have been motivated to co-administer with a glucocorticoid.

3. As of August 2006, a POSA Would Understand that Gerber's Use of "Glucocorticoid Replacement" with Ketoconazole Did Not Apply to Abiraterone Acetate

129. Gerber also does not provide any scientific reason to add prednisone to abiraterone acetate for any purpose. In Gerber, prednisone was used as glucocorticoid replacement therapy. (Ex. 1004 (Gerber) at 1179 (describing "the combination of ketoconazole and glucocorticoid replacement therapy"). As of August 2006, a POSA would understand that prednisone was given with

ketoconazole because it was known that ketoconazole caused clinical symptoms of adrenal insufficiency, because ketoconazole was a potent inhibitor of all adrenal steroid synthesis pathways. (Ex. 2090 (Tucker) at 2413-14; Ex. 2018 (Jubelirer) at 90; *see also* Ex. 1020 (Harris) at 544); Ex. 1080 (Lam) at 30).

130. But as explained above, a POSA would understand from O'Donnell and Barrie that abiraterone acetate did not inhibit all adrenal steroid synthesis, maintained normal cortisol levels, continued producing corticosterone, and did not result in any clinical symptoms of adrenal suppression. (*See supra* at ¶¶ 109-126). Therefore, as of August 2006, a POSA would understand that Gerber's use of glucocorticoid replacement with ketoconazole was not applicable to abiraterone acetate. The difference in the mechanism of action between the two compounds would have led to this conclusion as would have the difference in clinical effects.

4. As of August 2006, a POSA Would Not Have Given Glucocorticoids to Prostate Cancer Patients Unless There Was a Clear Clinical Need Because of Their Known Severe Side Effects and their Potential to Fuel the Cancer

131. As of August 2006, it was known that the administration of glucocorticoids, including prednisone, could result in severe adverse effects, including osteoporosis, immunosuppression, cardiovascular disease, and hypertension. (Ex. 2068 (Swartz) at 238, 243-247; Ex. 2069 (Seale) at 139-141). In my clinical experience up to this time, even short term use of glucocorticoids

was associated with severe side effects in patients, for example, hyperglycemia, steroid myopathy, gastrointestinal toxicity, and gastric bleed.

132. It was also known as of August 2006 that administration of exogenous glucocorticoids resulted in the suppression of ACTH release by the pituitary, which in turn caused regression of the adrenal cortex and loss of its ability to produce cortisol ("HPA axis suppression"). (Ex. 2068 (Swartz) at 242, 248; Ex. 2069 (Seale) at 141).

133. Because adrenal function is suppressed by the use of glucocorticoid therapy, if the glucocorticoid therapy is stopped suddenly, natural or endogenous production of glucocorticoids will be deficient. Moreover, glucocorticoid therapy inhibits the normal ability of the adrenal gland to produce excess glucocorticoids during a physiological stress. Depending on the level of suppression, it may take up to several months for the adrenal cortex to regain the capacity to synthesize normal and/or stress induced levels of cortisol, and in some instances, could even permanently damage the ability of the adrenal gland to make cortisol. (Ex. 2069 (Seale) at 141). Thus, if glucocorticoid replacement is given to a patient when it is not needed, it can have the paradoxical effect of causing adrenal insufficiency and/or diminishing adrenal reserve. (Ex. 2068 (Swartz) at 239)("In this setting, suppression of the hypothalamic-pituitary-adrenal axis may persist for as long as 9 to 12 months following steroid withdrawal if steroid doses are administered in the

supraphysiological range for longer than 2 weeks."); Ex. 2069 (Seale) at 141). Consequently, when a patient is receiving glucocorticoid replacement for a clinically diagnosed syndrome of adrenal insufficiency, their glucocorticoid dose is typically increased temporarily during times of physiologic stress to account for the fact that prolonged use of exogenous glucocorticoids will render them unable to naturally mount a cortisol response.

134. Indeed, it was known as of August 2006 that even single daily doses as low as 7.5 to 10 mg per day of prednisone will cause both toxic tissue effects and HPA axis suppression. (Ex. 2068 (Swartz) at 242; Ex. 2069 (Seale) at 139, 141). As a result, "it is not possible to stipulate a daily dose at which the risk of side-effects is non-existent." (Ex. 2069 (Seale) at 139).

135. As of August 2006, it was also known that exogenous steroid use had adverse effects with particular impact on mCRPC patients, including, for example, osteoporosis (which could exacerbate bone pain cause by bone metastases), immunosuppression (which could impede a patient's ability to fight the cancer and other illness), hypertension, muscle weakness, and steroid myopathy.

136. For example, a 2006 review article by Herr & Pfitzenmaier explains that in the presence of anticancer agents, glucocorticoids, including prednisone, substantially inhibited apoptosis (*i.e.*, cell death) in most types of solid tumors. Herr & Pfitzenmaier also suggest that glucocorticoid suppression of the immune

system may exacerbate the metastatic process and accelerate tumor growth and may increase risk of the development of other cancers. Further, they describe animal studies that showed that glucocorticoid treatment can increase the spread of some tumors. (Ex. 2023 (Herr & Pfitzenmaier) at *Abstract* ("[d]ata from preclinical and, to some extent, clinical studies, suggest that glucocorticoids induce treatment resistance in solid tumors, including prostate cancer"), 426-428).

137. Conde teaches that prostate cancer patients have significant bone loss, a higher incidence of bone fractures, and a high prevalence of osteopenia and osteoporosis, and that the continuous use of glucocorticoids presents a risk factor for osteoporosis in men because they cause bone loss. (Ex. 2025 (Conde (2003)) at 380, 382 ("[g]lucocorticosteroids are extensively used by elderly … [t]hese medications, however, causes [sic] bone (particularly trabecular bone) loss … Also, corticosteroid-related hypocalcemia directly stimulates PTH secretion, causing increased osteoclastic bone resorption").

138. Boumpas states that "[t]he benefits of glucocorticoid therapy can easily be offset by severe side effects; even with the greatest care, side effects may occur." (Ex. 2021 (Boumpas) at 1198). These side effects include steroid-induced osteoporosis. (*Id.* at 1205-06).

139. Moreover, as of August 2006, it was understood that glucocorticoids could actually promote the progression of prostate cancer by activating the

androgen receptor. For example, Krishnan described activation of a promiscuous mutant androgen receptor by cortisol, dexamethasone, prednisone, and corticosterone. (*See* Ex. 2024 (Krishnan) at *Abstract,* 1891-94, 1897-98). From these observations, the authors stated that "corticosteroids provide a growth advantage to prostate cancer cells harboring the promiscuous [mutant AR] in androgen-ablated patients and contribute to their transition to androgen independence." (*Id.* at *Abstract*; *see also id.* at 1899) (emphasis added).

140. The prior art also taught that continuous administration of even low doses of prednisone to patients with breast cancer demonstrated a statistically significant increase in bone and other metastases and second malignancies.[5] (Ex. 2060 (Marini) at *Abstract,* 247, 249). In this study, patients with breast cancer who received 7.5 mg/day of prednisone continuously for one year had an "increased incidence of bone [metastases]" and "increased cumulative incidence of second primary tumors." (*Id.* at 249). Based on these results, the researchers warned that "[t]he use of continuous, low dose prednisone is not recommended in the adjuvant setting [*i.e.*, after patients failed on primary cancer treatment]." (*Id.* at 249 (emphasis added)).

[5] In addition to prostate cancer, the '438 patent describes breast cancer. (Ex. 1001 at col. 1:20-55; col. 5:23-25).

141. Other researchers concluded that the Marini results are "even more disturbing that corticosteroids are more and more used in oncology.... it is appropriate to investigate the deleterious effects of the use of corticosteroids on bone metabolism in cancer patients, especially concerning a possible increase in the incidence of bone metastases." (Ex. 2061 (Body (1996)). Indeed, as of August 2006, a POSA would understand that the Marini results were of particular concern for prostate cancer, which was known to be "bone dominant." (Ex. 1025 (Harrison's) at 549).

142. As of August 2006, a POSA would understand the prior art teachings that glucocorticoids conferred a growth advantage to prostate cancer cells, that low dose prednisone increased bone metastases in patients, and the directive in Marini that prednisone "is not recommended," to clearly discourage the use of prednisone with abiraterone acetate in prostate cancer patients, and in mCRPC patients in particular.

B. There Was No Scientific or Clinical Basis in the Prior Art to Add Prednisone to Abiraterone Acetate to Address Mineralocorticoid Excess

1. As of August 2006, a POSA Would Understand that Ketoconazole Did Not Cause Mineralocorticoid Excess Syndrome or Symptoms of Hypertension, Hypokalemia, or Fluid Retention

143. Dr. Garnick argues that "the administration of ketoconazole was "known to reduce cortisol levels and potentially result in mineralocorticoid excess,

giving rise to side effects commonly associated with mineralocorticoid excess, including hypertension, hypokalemia, and fluid retention." (Ex. 1002 (Garnick Decl.) at ¶44 (citing Ex. 1003 (O'Donnell) at 2323; Ex. 1020 (Harris) at Abstract, 543; and Ex. 1023 (Attard) at 1242-43); *see also* Ex. 1002 (Garnick Decl.) at ¶78 (citing Ex. 1004 (Gerber) at Abstract, 1178-79; Ex. 1020 (Harris) at 542-543, 544; Ex. 1021 (Oh) at 90, Table III; Ex. 1027 (Costa-Santos) at 49, 57; Ex. 1025 (Harrison's) at 2143, 2145, 2146; Ex. 1026 (Auchus) at 104-105, 107, Ex. 1003 (O'Donnell) at 2318, Ex. 1023 (Attard (2005)) at 1242-43; Ex. 1028 (Jubelirer) at Abstract). Dr. Garnick's "mineralocorticoid excess" arguments are scientifically incorrect. Nothing in the prior art as a whole taught that ketoconazole caused mineralocorticoid excess syndrome or its associated side effects in patients. To the contrary, the prior art teaches the exact opposite.

144. First, Gerber does not mention mineralocorticoid excess, hypertension, hypokalemia, or fluid retention. (Ex. 1004 (Gerber)).

145. In addition, as discussed above, it was known as of August 2006 that ketoconazole due to its unselective mechanism of action, which includes the inhibition of the first step of converting cholesterol to pregnenolone, the required precursor for all adrenal steroids, ketoconazole inhibited all adrenal steroid pathways. Therefore, ketoconazole caused the under-production glucocorticoids

and mineralocorticoids. (Ex. 1003 (O'Donnell at 2318); Ex. 1020 (Harris) at 544; Ex. 1004 (Gerber) at 1177).

146. This under-production had been shown to result in clinical symptoms of adrenal insufficiency such as severe fatigue, weakness, weight loss, nausea, and vomiting, and low blood pressure (*i.e.*, hypotension), and the prior art taught that it was for this reason that ketoconazole was administered with glucocorticoid replacement therapy. (Ex. 2090 (Tucker) at 2413-14; Ex. 1028 (Jubelirer); Ex. 1025 (Harrison's) at 2141; *see also* Ex. 1020 (Harris) at 544; Ex. 1080 (Lam) at 30). Thus, the very prior art references cited by Dr. Garnick show that his opinions that ketoconazole caused mineralocorticoid excess are scientifically incorrect.

147. Jubelirer, Oh, Harris, and Attard cited by Dr. Garnick also do not support his opinions that the prior art taught that ketoconazole caused mineralocorticoid excess, hypertension, hypokalemia, or fluid retention in patients. Indeed, Dr. Garnick appears to be assuming that because these references discuss co-administration of ketoconazole with a glucocorticoid, they are somehow evidence that the purpose of the co-administration was given to treat mineralocorticoid excess. However, as I have already explained, this is scientifically incorrect. Further, as I discuss below, none of these references describe that any patient suffered from mineralocorticoid excess, or any symptoms such as hypertension, hypokalemia, or fluid retention.

148. The Jubelirer Abstract and full Jubelirer Article describe administration of ketoconazole as a single agent therapy to mCRPC patients, and teach that ketoconazole has "limited use" in mCRPC patients. (Ex. 1028 (Jubelirer Abstract); Ex. 2018 (Jubelirer Article) at 89). Neither the Jubelirer Abstract nor Article discuss mineralocorticoid excess, or any symptoms associated with it. The side-effects observed in patients treated with ketoconazole included nausea, vomiting, anorexia, rash, pruritus, transient abnormal liver function tests, and transient pulmonary infiltrates, however, none of the side-effects listed include hypertension, hypokalemia, and fluid retention. (Ex. 1028 (Jubelirer) *Abstract*; Ex. 2018 (Jubelirer Article) at 90). Indeed, the Jubelirer Article states that "[t]wo patients had adrenal insufficiency." (Ex. 2018 (Jubelirer Article) at 90). From this teaching, a POSA as of 2006 would understand that mineralocorticoid production following ketoconazole administration was reduced, not increased.

149. The Oh reference is a review of secondary hormonal therapies in prostate cancer that describes studies in which ketoconazole and hydrocortisone was administered to mCRPC patients. (Ex. 1021 (Oh) at 90). Oh lists symptoms relating to ketoconazole administration, including nausea, diarrhea, fatigue and skin changes, but does not describe mineralocorticoid excess, or any symptoms such as hypertension, hypokalemia, or fluid retention. (*Id.*)

150. Harris describes a Phase II clinical study where mCRPC patients were administered ketoconazole with hydrocortisone. (Ex. 1020 (Harris) at *Abstract,* 543). The toxicities observed in the study included (in order of prevalence): nausea, dry skin, fatigue, bruising, liver (hepatotoxicity), stomatitis (inflamed mouth), depression, and insomnia. (*Id.* at 542). Harris does not discuss mineralocorticoid excess, or the symptoms of hypertension, hypokalemia, or fluid retention.

151. Attard (2005) describes ketoconazole as "an imidazole antifungal agent that weakly and non-selectively inhibits several cytochrome P450 enzymes involved in adrenal steroid synthesis". (Ex. 1023 (Attard (2005)) at 1242). Attard (2005) does not describe mineralocorticoid excess or any symptoms associated with ketoconazole administration. Attard (2005) also does not discuss co-administration of ketoconazole with a glucocorticoid.

152. Indeed, because ketoconazole was a potent inhibitor of all adrenal steroids, ketoconazole was sometimes used off-label to manage symptoms associated with over-production of glucocorticoids and/or mineralocorticoids. For example, it was known that ketoconazole was used to decrease mineralocorticoids in patients who experienced symptoms associated with mineralocorticoid excess syndrome. (Ex. 2066 (Mantero) at *Abstract*, 82). In addition, ketoconazole was

used to manage symptoms of Cushing disease, which is characterized by the over-production of glucocorticoids. (Ex. 2065 (Farwell) at 1065).

153. The other prior art references cited by Dr. Garnick (Costa-Santos, Harrison's, Auchus) also do not support his opinions that the prior art taught that ketoconazole caused mineralocorticoid excess, hypertension, hypokalemia, or fluid retention in patients. These references do not discuss ketoconazole or prostate cancer. Rather, as I discuss in more detail below, I understand from Dr. Auchus that these references describe a congenital disease in children in which the gene encoding the CYP17 enzyme is mutated, resulting in variable impairment of CYP17's hydroxylase and lyase functions, resulting in a variety of clinical symptoms.

2. As of August 2006, Nothing in the Prior Art Would Have Suggested to a POSA that Abiraterone Acetate Would Cause Mineralocorticoid Excess

154. Dr. Garnick also attempts to argue that it was known in the prior art that "CYP17 inhibition of cortisol increased ACTH drive (*i.e.*, increased ACTH production), which resulted in a corresponding increase in mineralocorticoids." Further, Dr. Garnick argues that it was known to administer a glucocorticoid such as hydrocortisone or prednisone to suppress ACTH drive such that "fewer mineralocorticoids are produced and the adverse side effects of hypertension, hypokalemia, and fluid retention are reduced in the presence of CYP17 inhibition."

(Ex. 1002 (Garnick Decl.) at ¶¶41-42) (citing Ex. 1027 (Costa-Santos) at *Abstract*, 49; Ex. 1026 (Auchus (2001)) at *Abstract*; and Ex. 1025 (Harrison's) at 2143, 2145-46).

155. To the extent that Dr. Garnick seeks to rely upon these teachings to support his argument that a POSA would have been motivated to co-administer prednisone with abiraterone acetate for purposes of "safety and tolerability" (*see, e.g.*, Ex. 1002 (Garnick Decl.) at ¶¶ 44, 58), I disagree. As of August 2006, nothing in the prior art related to ketoconazole or abiraterone acetate would have suggested to a POSA that administration of abiraterone acetate would cause clinical manifestations of mineralocorticoid excess syndrome.

156. As of August 2006, a POSA would understand that there was nothing in O'Donnell or the Barrie patent that taught or suggested that abiraterone acetate causes ACTH drive, mineralocorticoid excess, hypertension, hypokalemia, or fluid retention. O'Donnell does not even discuss these. (Ex. 1003 (O'Donnell) at 2322). In fact, patient mineralocorticoid levels were not measured in the O'Donnell studies. (*Id.*)

157. As discussed, O'Donnell also reports that abiraterone acetate was "very well tolerated" and "no alteration in resting heart rate or blood pressure was seen." (*Id.* at 2322). If anything, the fact that blood pressure levels remained

normal would have suggested to POSA that mineralocorticoid excess did not occur.

158. In addition, O'Donnell reported that patients' cortisol levels remained within normal limits. (*Id.* at 2320-2323).

159. The Barrie patent likewise does not discuss glucocorticoid replacement, ACTH drive, mineralocorticoid excess, hypertension, hypokalemia, or fluid retention. (Ex. 1005 (Barrie)).

160. I also understand from the declaration of Dr. Auchus that as of August 2006, a POSA would also have understood that the Costa-Santos, Auchus and Harrison's references (the other references cited in Dr. Garnick's declaration) did not teach or suggest that administration of abiraterone acetate would cause mineralocorticoid excess. (Ex. 2040 (Auchus Decl.) at ¶ 49).

161. Dr. Auchus explains that these publications describe genetic defects in CYP17's 17α-hydroxylase/17,20-lyase activity that resulted in an increased production of mineralocorticoids. For example, the Auchus publication describes mutations of the CYP17 gene in which the CYP17 enzyme is completely absent, resulting in "combined 17α-hydroxylase activity/C17,20-lyase deficiency." This mutation prohibits the production of cortisol, resulting in increased ACTH and mineralocorticoids, which causes clinical symptoms of hypertension, hypokalemia, and fluid retention. (*Id.* at ¶¶ 49-63).

162. By contrast, as Dr. Auchus explains in his declaration, there was no evidence in the prior art to show that abiraterone acetate administration prohibits the production of cortisol so as to cause mineralocorticoid excess. To the contrary, O'Donnell teaches that cortisol continued to be made following abiraterone acetate administration, which "remained within normal limits," and abiraterone acetate "was very well tolerated." (*Id.* at ¶ 20-26, 27-32; Ex. 1003 (O'Donnell) at 2320-2323).

163. Indeed, Dr. Auchus explains that because O'Donnell teaches that cortisol production still occurred following abiraterone acetate administration, as of August 2006, a POSA would understand abiraterone acetate's mechanism of action to be similar to that of "isolated 17,20-lyase deficiency," a type of congenital CYP17 deficiency in which CYP17's 17α-hydroxylase activity is relatively preserved, cortisol production still occurs, and the patients "do not show the consequences of mineralocorticoid excess because preserved cortisol production prevents excessive [mineralocorticoid] accumulation." (Ex. 2040 (Auchus Decl.) at ¶ 62-63; *see also* Ex. 1005 (Barrie) at col. 21:25-66 to col. 22:65).

3. Even if Mineralocorticoid Excess Was Observed, As of August 2006, a POSA Would Understand that It Could Be Managed Without Glucocorticoid Replacement

164. As of August 2006, a POSA would understand that there were numerous strategies available for managing a patient's symptoms of mineralocorticoid excess (*i.e.*, hypertension, hypokalemia, and fluid retention), including mineralocorticoid antagonists, anti-hypertensives, diuretics, sodium restriction and oral potassium supplements, that did not have the severe toxicities associated with glucocorticoid replacement. If a prostate cancer patient experienced symptoms of mineralocorticoid excess, glucocorticoids and their many known toxicities would have been avoided in favor of using mineralocorticoid antagonists, such as eplerenone, anti-hypertensives, diuretics, sodium restriction, oral potassium supplements, or a combination thereof to address the unique set and severity of symptoms being experienced by the patient.

165. In 2006, a POSA would have known that eplerenone, a mineralocorticoid antagonist, was the most logical choice for managing symptoms related to a clinical syndrome of mineralocorticoid excess. In 2002, the FDA approved the mineralocorticoid antagonist drug INSPRA® (Eplerenone) for the treatment of hypertension. (Ex. 2062 (Craft) at 217). It was known to be safe and effective for the long-term, continuous treatment of chronic hypertension, alone or in combination with other agents, with minimal side effects. Mineralocorticoid

antagonist drugs such as eplerenone act by blocking the binding of mineralocorticoids at the mineralocorticoid receptor. (*Id.*) Because of its known mechanism of action, eplerenone would have been the most targeted approach for managing any and all of the symptoms associated with a clinical syndrome of mineralocorticoid excess.

166. In addition, anti-hypertensive drugs and diuretics were widely available and had been commonly used for decades to manage hypertension and fluid retention, including in men with prostate cancer, with minimal side effects. Depending upon the severity, hypertension and fluid retention could also be managed using dietary sodium restriction or diuretics, also well-known and commonly used strategies for managing these clinical symptoms. Additionally, potassium levels could be monitored and if they fell below the normal range, oral potassium supplements could be administered. (Ex. 2066 (Mantero) at 84-85).

C. There Was No Scientific or Clinical Basis for Believing that the Combination of Abiraterone Acetate and Prednisone Could Be Successful in Achieving the Inventions Claimed in the '438 Patent

1. As of August 2006, the Prior Art Did Not Teach that Ketoconazole was "Safe and Effective" for the Treatment of mCRPC

167. I understand that Mylan's expert, Dr. Garnick, has stated in his declaration that "[ketoconazole] was commonly used off-label . . . in combination with prednisone or hydrocortisone to treat mCRPC." (Ex. 1002 at ¶33). I also

understand that Dr. Garnick has stated that "[ketoconazole] . . . was known to be effective as a second-line treatment for mCRPC." (*Id.* at ¶43). In addition, I understand that Dr. Garnick has stated that "[Gerber teaches that] the combination of ketoconazole and prednisone is safe and effective in treating patients with mCRPC." (*Id.* at ¶¶35, 67), and further argues that Gerber teaches "to co-administer 10 mg/daily of prednisone in combination with ketoconazole for the treatment of hormone refractory metastatic prostate cancer." (Ex. 1002 (Garnick Decl.) at ¶¶ 58-59). I disagree with all four of these statements.

168. Dr. Garnick's conclusions concerning Gerber are scientifically incorrect and misleading. By 2006, a POSA would understand that Gerber was a retrospective collection of patients' charts, without any organized approach regarding how patients were managed, treated and followed, and reporting PSA declines that a POSA in 2006 would not consider to be clinically relevant. In addition, importantly, by 2006 it was well-understood that ketoconazole co-administered with a glucocorticoid did not improve overall survival and was never FDA-approved for the effective treatment of prostate cancer.

169. By 1990, it was established that medical and surgical castration offered similar clinical benefit to patients. Despite these advances, most castrated patients with metastatic disease eventually relapsed. In 1990, there were no FDA approved treatment options available for patients with hormone refractory

metastatic prostate cancer, and no treatment had shown a survival benefit for patients in a controlled clinical trial. As a result, clinicians and researchers, desperate to offer patients some type of treatment and to find a drug that could control the growth of the cancer and extend survival, were experimenting with off-label uses of available drugs.

170. The drug combination described in Gerber, ketoconazole and prednisone, was one such off-label use. As Gerber explains, ketoconazole was originally developed as an anti-fungal agent. (Ex. 1004 at 1177). However, it was also observed that ketoconazole is a potent inhibitor of gonadal and adrenocortical steroid synthesis and that it had an *in vitro* cytotoxic effect on prostate cancer cells. (*Id.*). In men with hormone refractory prostate cancer, however, results with ketoconazole had not been promising. For example, Gerber describes Jubelirer *et al.* as concluding that ketoconazole "has limited use in patients who have failed prior hormonal therapy for advanced prostate cancer." (*Id.* at 1179). At the same time, however, there were rare reports in the literature suggesting that a small subset of patients with hormone refractory prostate cancer experienced some signs of brief disease regression using measurements of tumor mass or bone scan, but did not provide a survival benefit (*Id.* at 1179). Indeed, no approved options were available for hormone-refractory prostate cancer patients that increased survival. However, ketoconazole was not "commonly used" for treating hormone refractory

prostate cancer patients and was considered a "last resort" therapy for patients who had failed other available options.

171. As of August 2006, a POSA would not have understood Gerber to teach or suggest that the combination of ketoconazole and prednisone was "safe and effective." A POSA also would not have understood that Gerber taught that administration of ketoconazole in combination with 5 mg prednisone twice daily "is safe and effective in treating human patients with hormone-refractory prostate cancer."

172. In order to properly evaluate whether a new therapy is safe or effective, the safety or efficacy (or both) of the therapy should be evaluated using a well-controlled randomized clinical trial. In particular, a study protocol is required that prospectively defines the purpose of the study, the selection criteria for study participants, the duration of treatment and evaluation periods, and response criteria (including describing reliable methods for observing and quantifying the response criteria). Also, side effects must be carefully monitored and documented. Adherence to the protocol is required and any modifications should not only be documented, but also analyzed to determine their potential impact on the results. Any report of the findings should describe the results and the analytic methods used to evaluate them, including the statistical methods used. (*See* Ex. 2048 (Altman) at Table 2).

173. Gerber does not satisfy any of these requirements, and does not report the results of an actual prospective clinical trial. Gerber reports the data collected from a retrospective review of patient charts without any organized approach to how patients were managed, treated, and followed or how they came to be included in the analysis. As an initial matter, Gerber does not show that any clinical trial protocol was followed. Nor does it set forth any specific criteria for patient selection, the duration of treatment and evaluation periods, or response criteria (including describing reliable methods for observing and quantifying the response criteria), the measurement of adverse effects, nor the analytical methods used to analyze any results. By way of example, no patient inclusion or exclusion criteria are specified for the 15 patients described in Gerber. Rather, the authors retrospectively described the commonalities and differences between the patients whose results were being reported. Patients appear to have had a variety of disparate prior treatments. (Ex. 1004 (Gerber) at 1178). Fourteen out of the fifteen patients had undergone orchiectomy at least 5 months before participation, but one had been treated with injections of a luteinizing hormone releasing hormone agonist for 17 months before participation. (Ex. 1004 (Gerber) at 1177). In addition, 10 of the 15 patients previously received radiotherapy. Twelve "had bone pain and/or other symptoms of widespread malignancy," and the remaining three

were asymptomatic. (*Id.*). These prior treatments could have influenced the observed "response" to ketoconazole and prednisone.

174. Gerber states that patients were initially administered "600 mg to 900 mg ketoconazole daily in 3 divided doses and 5 mg prednisone twice per day," and that "the ketoconazole dosage was increased to 1200 mg daily in 3 divided doses if the PSA did not decrease." (*Id.* at 1178). However, Gerber does not describe how often the higher dose was administered. Also, all the patients received the drug combination, and there was no control for a placebo effect of either drug. Without any control, any conclusions reported in Gerber would have been understood by a POSA to be, by definition, unscientific.

175. Gerber states that at each visit patients "underwent history and physical examination, and they were specifically questioned regarding treatment-related side effects. Liver function tests were evaluated along with each serum PSA level." (*Id.* at 1178). However, Gerber does not describe any criteria for the objective measurement of side effects or attempts to monitor patients' compliance to the dosage schedule or use of other medications, including analgesics. Therefore, the use of analgesics or other concomitantly administered medications could have affected the patients' responses or the side effects they experienced.

176. Gerber reported that 2 out of the 15 patients (13%) "suffered minor bruising believed to be secondary to prednisone." (*Id.* at 1179). Although Gerber

reports that liver functioning and blood chemistry was monitored, and patients were questioned regarding side-effects, this limited evaluation is insufficient to demonstrate the "safety" of ketoconazole and prednisone.

177. Gerber reports that of the 15 patients, 12 (80%) had a decrease in PSA with a median duration of response of 3 months. (*Id.* at Abstract, 1178). Gerber also reports that in 9 of 12 men, the improvement in PSA was "short-lived (i.e., less than or equal to four months) and "occasionally of small magnitude," but it did correlate with subjective improvement in symptomatic patients in all but 1 instance. (*Id.* at 1179). More specifically, of the 12 patients who had bone pain and/or other symptoms of advancing malignancy prior to administration of ketoconazole and prednisone, nine (75%) reported subjective improvement, however, these were not validated either by documenting patients use of analgesics or by documenting in an objective fashion what kind of subjective improvement occurred. One patient had a 7% decrease in PSA during four months of treatment but he had no improvement in bone pain. (*Id.* at 1178). However, 1 of the 3 patients who had no decrease in PSA levels also reported a transient decrease in bone pain. (*Id.* at 1178).

178. Gerber does not report objective criteria, such as reduction in measureable tumor size or improvements in bone scan abnormalities, to evaluate the regression of the patient's prostate cancer. Furthermore, although the patients

were asked about any perceived improvements in their bone pain, there was no standardized survey or objective measures used to evaluate patients' bone pain while on ketoconazole and prednisone. As a result, the bone pain data reported was highly subjective and subject to a great degree of variability. With respect to the PSA levels that were measured, the data reported in Gerber would have provided little, if any, guidance to a POSA with regards to the efficacy of the methods.

179. While Gerber states that "PSA levels were recommended monthly," the recommendations do not appear to have been consistently followed as reflected in Figures 1-3, which show that PSA measurements were performed at a variety of different time periods. (*Id.* at 1178 Figs. 1-3). Moreover, in the Gerber report, any PSA decrease was considered to be a "response." For example, Gerber reports that the mean decrease in PSA in the 12 "responding" patients was 49% of the pre-treatment level. (*Id.* at 1178). Because PSA decrease was reported as a mean value in Gerber, the average PSA response could have been driven by just a few outlier values, and the median value could have been much lower. For example, a patient with a PSA decline of 7% was reported as a "responding patient." (*Id.*). Thus, in Gerber, patients in the "responding" group included those who had a PSA decrease of greater than 50%, as well as those who had a PSA decrease of less than 50%. It is impossible to determine based on Gerber how many patients experienced a PSA decline of greater than 50%.

180. But, as of August 2006, the Prostate Cancer Working Group guidelines defining a PSA "response" as a PSA decline "of at least 50%, which must be confirmed by a second PSA value 4 or more weeks later" were well-accepted. (*See supra* at ¶64). Publications that reported a PSA decline of less than 50% as a "response" were not given much weight and were often repeated or superseded by studies that applied the Working Group guidelines. Therefore, as of August 2006, a POSA would have concluded that PSA "responses" reported in Gerber, which reported any decline in PSA as a response, and did not include any other objective response criteria, did not provide any guidance concerning the efficacy or safety of ketoconazole and prednisone in mCRPC patients, and would not have given the results much weight.

181. Further, Gerber itself concludes that "[s]hort-term decreases in PSA are of unclear importance but probably do not reflect significant disease regression" and "it is unlikely that significant impact on survival will be seen in these cases." (Ex. 1004 (Gerber) at 1179).

182. Gerber reports that two patients had longer term declines in PSA of greater in 50% (Ex. 1004 at 1178), but does not provide any radiographic evidence or survival data to confirm that these patients experienced a clinical benefit. In light of the methodological deficiencies in Gerber and the absence of confirmatory tumor response data, a POSA would not have been able to conclude based upon

results in only 2 patients that ketoconazole and prednisone was safe and effective for the treatment of mCRPC.

183. Therefore, for all the reasons stated above, a POSA reading Gerber in August 2006 would understand that the paper's conclusion that "there appears to be a small subgroup of patients who will derive significant benefit from the combination of ketoconazole and glucocorticoid replacement therapy" overstated the observed outcomes because the results reported do not justify such a statement, and that the results of Gerber were, at best, inconclusive.

184. My opinions are confirmed by other contemporaneous references. Following its publication, other researchers commented on the limitations of the Gerber results. In a December 1991 Letter to the Editor, Dr. Clyde Blackard of the Park Nicollet Medical Center, Minneapolis, Minnesota, noted that the decreases in PSA levels reported in Gerber likely did not reflect clinical improvement:

> It is likely that the effects of ketoconazole and prednisone in decreasing PSA levels <u>have little or nothing to do with clinical improvement</u>.

(Ex. 2049 (Blackard) at 1621) (emphasis added). Dr. Blackard also stated that the observed reductions in bone pain were "largely subjective and difficult to evaluate" and could have been related partly to bed rest and simultaneously administered analgesics. (*Id.* at 1621). Dr. Blackard further emphasized that none of the 15 patients "showed a significant improvement in terms of increased survival,"

concluding that "[w]e definitely need more research in this area." (*Id.*) Dr. Blackard's 1991 letter of response to the Gerber paper reflects the pressing concern shared among clinicians at the time that experimental treatments for refractory prostate cancer consistently failed to meet the ultimate goal of improving survival.

185. The authors of Gerber published a response to Dr. Blackard, which acknowledged that "we have insufficient data to determine the impact on survival." (*Id.* at 1622).

186. Other prior art references citing to Gerber also confirm that a POSA would not have understood Gerber to teach that ketoconazole, alone or in combination with prednisone, was "safe and effective." (*See* Ex. 2053 (Lara) at 140) (noting Gerber's short response to PSA and "no improvement in overall survival"); Ex. 2054 (Kuzel) at 1965) (noting the short duration of PSA response in Gerber); Ex. 2055 (Scher) at 2928 (noting that ranges of response rates to second and third line hormonal therapies is "less clear because a range of response proportions have been reported" which is "the result of patient and tumor related factors"); and Ex. 2056 (Sternberg) at 331 (citing Gerber to say "[w]hile changes in PSA are a good indicator of disease activity in men with metastatic prostate cancer treated with hormonal manipulation, the role in patients treated with second line therapy is less clear")(emphasis added).

187. Indeed, ketoconazole, alone or in combination with prednisone, was never approved by the FDA for prostate cancer treatment and its use in Gerber was "off-label." By the early 2000s, ketoconazole in combination with a glucocorticoid, such as hydrocortisone or prednisone, had failed to show any survival benefit in mCRPC patients in Phase II and Phase III clinical trials. (Ex. 1021 (Oh) at 91; Ex. 2063 (Small) at 1031("no difference in survival was observed" for patients treated with either anti-androgen withdrawal alone or antiandrogen withdrawal plus simultaneous ketoconazole and hydrocortisone replacement therapy); Ex. 2064 (Millikan) at 115 ("we found no evidence that either of these regimens [ketoconazole and hydrocortisone or ketoconazole, hydrocortisone, and doxorubicin] is likely to substantially improve the survival of patients with androgen independent prostate cancer"). I understand that Dr. Garnick has agreed that ketoconazole has never been demonstrated to have any survival benefit.

188. These studies confirmed that ketoconazole offered, at best, a last-resort therapeutic option for such patients, particularly in view of the fact that docetaxel –based chemotherapy was the first (and only) therapy shown to improve overall survival in patients with mCRPC. Ketoconazole has never been approved by the FDA for prostate cancer treatment because no randomized trial has shown it

to be either safe and/or effective for patients with mCRPC. If anything, this failure confirms that the subject matter of the claims was not obvious in August 2006.

2. The Prior Art Did Not Provide a Scientific or Clinical Basis for Believing that Prednisone Would be Effective for Treating Cancer

189. I understand that Dr. Garnick has testified that "it is my experience in clinical practice . . . that the administration of prednisone alone does not have any clinically significant anti-cancer or anti-tumor effect, especially when compared to and dosed with a compound like abiraterone. Furthermore, in my experience, no treating physician would prescribe prednisone alone as an anti-cancer or anti-tumor agent to a patient with prostate cancer." (Ex. 1002 (Garnick Dec.) at ¶89). I agree with this testimony, as it is consistent with my clinical experience and expertise.

190. As of August 2006, nothing in the prior art taught or suggested that the prior art taught "a therapeutically effective amount of prednisone," which the Panel construed to mean "an amount of prednisone effective for treating prostate cancer," where "treating" means "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." In fact, a POSA would have known that randomized clinical trials failed to establish that glucocorticoids such as prednisone improve survival. Ex. 1021 (Oh) at 91; Ex. 2063 (Small) at 1031; Ex. 2064 (Millikan) at 115. As a result, a POSA would have

been skeptical, based on prior experience with glucocorticoids, that prednisone would provide any anti-cancer benefits for treating prostate cancer. In particular, none of O'Donnell, Barrie, or Gerber teach or suggest that glucocorticoids (including prednisone) were effective for treating prostate cancer, alone or in combination with another drug, nor do they suggest that prednisone would enhance and prolong the efficacy of abiraterone acetate.

191. O'Donnell does not teach or suggest administering a "therapeutically effective amount of prednisone." O'Donnell does not mention prednisone, and the O'Donnell patients "were not allowed to take concomitant steroids." (Ex. 1003 (O'Donnell) at 2319). Furthermore, to the extent O'Donnell discusses glucocorticoids, it is only as replacement therapy, which was not found to be necessary with abiraterone acetate.

192. Barrie also does not teach or suggest administering a "therapeutically effective amount of prednisone." Glucocorticoids were not administered in the animal studies reported in Barrie and it does not discuss any therapeutic benefit of a glucocorticoids. (Ex. 1005 (Barrie)).

193. In Gerber, prednisone was given along with ketoconazole as glucocorticoid replacement. Further, for the reasons explained above in Section VIII.C.1, a POSA would not have interpreted the results in Gerber as providing

evidence of any clinical efficacy of prednisone for the treatment of prostate cancer. (Ex. 1004 (Gerber)).

IX. REAL WORLD FACTS OR "OBJECTIVE INDICIA OF NON-OBVIOUSNESS" SUPPORT THE NON-OBVIOUSNESS OF THE '438 PATENT INVENTION

A. The Invention Claimed in the '438 Patent Resulted in Unexpected Clinical Efficacy

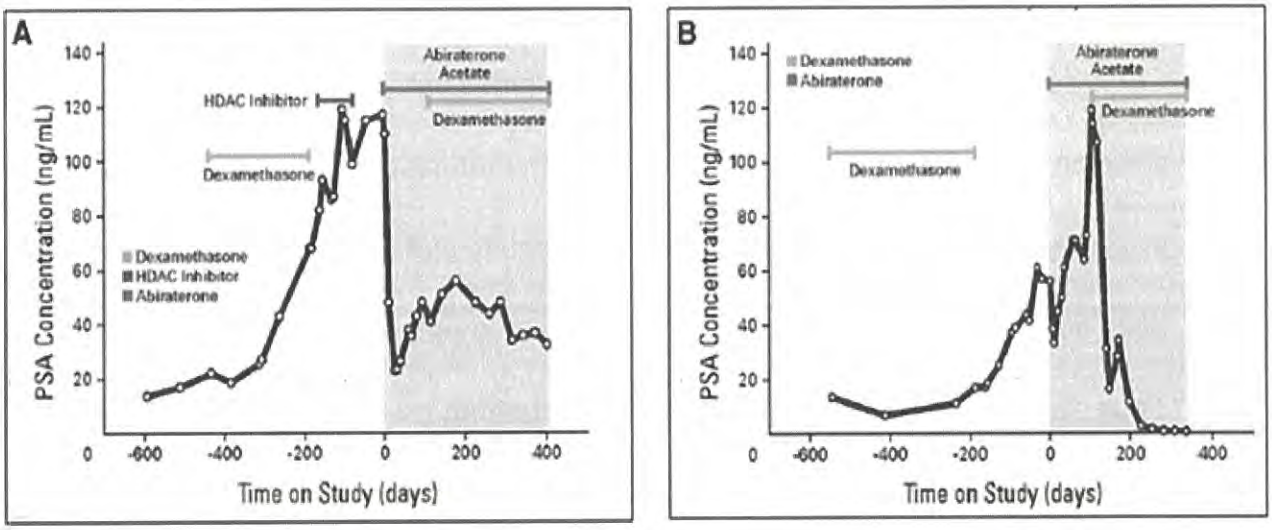
194. I have reviewed Attard *et al.*, "Phase I Clinical Trial of Selective Inhibitor of CYP17, Abiraterone Acetate, Confirms That Castration-Resistant Prostate Cancer Commonly Remains Hormone Driven," *J. Clin. Oncol.*, 2008; 26(28):4563-4571, (Ex. 2014 (Attard (2008)).

195. I have also reviewed Attard *et al.*, "Selective Inhibition of CYP17 With Abiraterone Acetate Is Highly Active in the Treatment of Castration-Resistant Prostate Cancer," *J. Clin. Oncol.*, 2009; 27(23):3742-3748, (Ex. 2015 (Attard 2009)).

196. The Attard (2008) and Attard (2009) publications show that the use of abiraterone acetate and prednisone in combination results in increased efficacy by avoiding clinical resistance to abiraterone acetate and decreasing steroid precursors that can activate androgen receptor signaling and promote prostate cancer growth. Thus, the efficacy of abiraterone acetate in treating prostate cancer is maximized through its concomitant administration with prednisone.

197. More specifically, Attard (2008) and Attard (2009) describe an "extension study" that was included in the first Phase I/II abiraterone acetate clinical trial. The "extension study" was prospectively designed to allow the addition of a glucocorticoid (dexamethasone) to abiraterone acetate in patients at disease progression (*i.e.*, in patients who experienced a benefit from abiraterone acetate, but who stopped responding and whose cancer began to grow again). The purpose of the "extension study" was to test the hypothesis that resistance to abiraterone acetate could be reversed by decreasing upstream androgenic steroids that could activate the androgen receptor. (Ex. 2014 (Attard (2008)) at 4565, 4568-70, Appendix A1; Ex. 2015 (Attard 2009) at 3743, 3745-47).

198. The figure below, adopted from Attard (2008) (Ex. 2014, Fig 1-Appendix A1, Figure 2), illustrates the results from the extension study.



199. The data show patients who had progressed on abiraterone acetate alone (*i.e.*, who had experienced a rise in PSA levels) showed clinical improvement (*i.e.*, a subsequent drop of PSA) when a glucocorticoid was added in combination with abiraterone acetate therapy.

200. In addition, patients who previously had progressed on glucocorticoid therapy before they received abiraterone acetate, were initially treated with abiraterone acetate as a monotherapy; when these patients progressed on abiraterone acetate treatment alone, a glucocorticoid was added to the abiraterone acetate, and the patients saw a clinical improvement, including PSA declines of greater than 50%. (Ex. 2014 at 4568-69, Appendix – Fig. A1).

201. These results helped validate the hypothesis that the combination of a glucocorticoid and abiraterone acetate result in an anti-cancer activity beyond the effects of either therapy alone. The study employed a clever design in which each patient served as his own control – the patient received both agents as single agents and then the combination of agents, and the results of the three sequential interventions in the single patient was compared. The study design allowed researchers to rule out dexamethasone or abiraterone acetate as being individually responsible for PSA responses in the patient, since the patients receiving the combination of abiraterone acetate and dexamethasone had already previously progressed on each agent alone. This "n of 1" study design allows for

interpretation of results without requiring researchers to enroll a large number of patients to achieve a statistically significant p-value. Instead, when each patient serves as his own control, meaningful information can be learned by examining individual patient responses.

202. The results of the extension study established a beneficial therapeutic effect in the co-administration of abiraterone acetate and a glucocorticoid. A POSA would understand the dexamethasone extension study results to be due to a class effect of glucocorticoids, and thus a POSA would understand these findings to apply to the use of any glucocorticoid in combination with abiraterone acetate. I understand that these results were incorporated into the COU-AA-004 clinical trial protocol, which is the first clinical trial specifically designed to evaluate combination therapy involving abiraterone acetate and prednisone in patients with mCRPC. (Ex. 2118 (de Bono Decl.) ¶12; Ex. 2016 (Danila) at 1497).

203. The unexpected clinical benefits of the combined administration of administration of abiraterone acetate and a glucocorticoid were further demonstrated in additional Phase I-II clinical trial results, as measured by the time to PSA progression in chemotherapy-naïve patients.

204. Table 1 below shows that patients who received abiraterone acetate as a monotherapy had a median time to PSA progression of 7.5 months. (Ex. 2015 (Attard (2009)) at 3745). Patients who initially received abiraterone acetate

monotherapy but subsequently progressed and then received the combination of the glucocorticoid dexamethasone and abiraterone acetate, had a median time to PSA progression[6] of 12.4 months or 12 months (two patient groups were defined according to prior treatment before the study with dexamethasone). (*Id.* at 3743, 3745-3746).

205. Thus, there was an increased (improved) time to PSA progression of about 5 months when glucocorticoids were added to the treatment regimen upon progression following abiraterone acetate monotherapy. Surprisingly, however, Table 1 also shows that when abiraterone acetate was administered in addition to prednisone from the start, there was a median time to PSA progression of 16.3 months, *i.e.*, these patients on average responded for *more than twice as long* as patients on abiraterone acetate monotherapy. (Ex. 2017 (Ryan (2011)) at 4856-4857). This result could not have been predicted in advance.

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[6] Time to PSA progression was measured from the start of abiraterone acetate monotherapy to the end of the combination therapy. (Ex. 2015 (Attard (2009) at 3746).

Table 1

Clinical Trial	Patient group	Treatment	Time to PSA Progression	Source
COU-AA-001	Chemo-naïve	Abiraterone acetate monotherapy	7.5 months (225 days)	Ex. 2015 Attard *et al.* (2009), at 3745.
COU-AA-001	Chemo-naïve Dexamethasone naïve	Abiraterone acetate + dexamethasone at progression	12 months (361 days)	Ex. 2015, Attard *et al.* (2009), at 3743, 3745-3746.
COU-AA-001	Chemo-naïve Previously failed dexamethasone monotherapy	Abiraterone acetate + dexamethasone at progression	12.4 months (372 days)	Ex. 2015, Attard *et al.* (2009), at 3743, 3745.
COU-AA-002, Amendment 5	Chemo-naïve	Abiraterone acetate + prednisone from the start	16.3 months	Ex. 2017, Ryan *et al.* (2011), at 4856-4857.

206. While head-to-head comparisons in a randomized, adequately powered placebo-controlled Phase III clinical trial are the highest standard in evaluating comparative efficacy of two prostate cancer therapies, clinical trial results from different studies are often compared in the literature and in clinical

practice to ascertain trends in relative effectiveness of different therapies when study populations and endpoints are comparable.

207. A comparison of the results of the Attard (2009) and Ryan (2011) studies is compelling due to the multiple independent patient prognostic factors, many of which were similar, and the similarities of the study design and endpoints described in both publications. In both studies, patients enrolled were chemotherapy-naïve, had ECOG scores of 0 or 1 and a median Gleason score of 8, which are measures reflecting disease severity. (Ex. 2015 (Attard 2009) at 3744, 3746; Ex. 2017 (Ryan 2011) at 4856). 79% and 76% of patients, respectively, had bone metastases. (*Id.*) These similarities suggest that the patients enrolled in both studies may have had comparable disease burden.

208. Although there were some differences in reported baseline PSA between the two studies, I would not expect these differences to account for the marked improvement in time to PSA progression reported for patients when abiraterone acetate was used in conjunction with prednisone as compared to abiraterone acetate monotherapy.

209. The unexpected finding that the efficacy of abiraterone acetate in treating prostate cancer is maximized through its concomitant administration with prednisone, as demonstrated by a comparison of the clinical evidence observed when abiraterone acetate is administered as a monotherapy versus when

abiraterone acetate is co-administered with a glucocorticoid, such as prednisone, shows that in ZYTIGA® combination therapy, prednisone *and* abiraterone acetate each contribute to the anti-cancer effects.

210. Subsequently, I understand that two Phase III clinical trials were performed with the combination of abiraterone acetate and prednisone. Study 1 enrolled mCRPC patients who had received prior docetaxel chemotherapy. (Ex. 1034 (de Bono) at *Abstract*, 1996). The results showed that overall survival was longer in the abiraterone acetate-prednisone group than in the placebo-prednisone group. (*Id.* at *Abstract*, 1998-99). Based upon Study 1, in April 2011, the FDA approved the use of abiraterone acetate in combination with prednisone for the treatment of mCRPC patients who had received prior docetaxel chemotherapy. (Ex. 2070 (FDA News Release (2011)).

211. Study 2 enrolled mCRPC patients who had not received prior cytotoxic chemotherapy. (Ex. 1009 (Ryan) (2013) at *Abstract*, 139-40). The results showed that abiraterone acetate in combination with prednisone improved radiographic progression-free survival in these patients. (*Id.* at 141-143, 145-147). In the final analysis of the data of this study, there was a statistically significant overall survival benefit as well. (Ex. 2071 (Ryan 2015) at *Abstract*, 157-159).

212. Based upon Study 2, in December 2012, the FDA approved the use of abiraterone acetate in combination with prednisone for the treatment of mCRPC

patients who had not received prior docetaxel chemotherapy. (Ex. 1045 (FDA News Release (2012)).

213. The use of abiraterone acetate in combination with prednisone for the treatment of patients with mCRPC is the first oral, non-cytotoxic, secondary hormonal therapy to show a survival benefit in patients with mCRPC.

B. The Invention Claimed in the '438 Patent is Embodied in ZYTIGA® Therapy and Contributes Significantly to the Success of ZYTIGA®

214. ZYTIGA® is a prescription medicine that is indicated in combination with prednisone for the treatment of patients with mCRPC. (Ex. 1065 (ZYTIGA® Full Prescribing Information) at 1) (hereinafter "ZYTIGA® therapy").

215. I have been asked to consider whether the treatment of patients with ZYTIGA® therapy as described in the FDA-approved label would be covered by claims 1-20 of the '438 patent. In my opinion, such treatment would be covered by those claims. More specifically, the prescribing information for ZYTIGA® shows that FDA-approved use of ZYTIGA® includes each and every element of claims 1-20 of the '438 patent, including: a method for the treatment of prostate cancer in a human; administering to said human a of therapeutically effective amount of abiraterone acetate and a therapeutically effective amount of prednisone; the claimed dosages of abiraterone acetate and prednisone; the claimed dosage forms; refractory prostate cancer, wherein the refractory prostate cancer is not responding

to an anti-cancer agent; and the recited anti-cancer agents. Castration-resistant prostate cancer is "refractory prostate cancer." Anti-androgens are commonly used with hormonal ablation agents. (*Id.* at Indications and Usage; Dosage and Administration Recommended Dosage; Dosage Forms and Strengths; Description; Clinical Trial Experience; Clinical Studies; How Supplied; Patient Counseling Information).

216. Further, claims 19 and 20 are specifically directed to the FDA-approved method of using ZYTIGA. Claim 19 of the '438 patent recites the specific elements of the FDA-approved method of use of ZYTIGA® in patients who have not received prior cytotoxic chemotherapy. Claim 20 of the '438 patent recites the specific elements of the FDA-approved method of use of ZYTIGA® in patients who have received prior docetaxel chemotherapy.

217. Based upon the clinical evidence I have reviewed concerning the unexpected benefits of the invention claimed in the '438 patent (*see supra* at Section IX.A), it is my opinion that the therapeutic effect of abiraterone acetate in treating mCRPC is unexpectedly enhanced with the addition of prednisone, *i.e.*, the evidence shows that in ZYTIGA® therapy, prednisone has a therapeutic effect in treating mCRPC. This scientific evidence supports the conclusion that, when ZYTIGA® therapy is administered to mCRPC patients, prednisone and abiraterone acetate each have the effect of "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."

218. Based upon my clinical experience, in the case of mCRPC, it is my opinion that physicians and patients value anti-tumor effects as the key treatment attribute to consider. Further, in the realm of mCRPC drug development, the primary emphasis is the improvement in survival, which is a goal of clinicians, researchers, and patients. Patients are typically willing to accept a diminished quality of life to improve quantity of life. Physicians and patients evaluate efficacy of mCRPC treatments based upon survival, with a patient's PSA response and radiographic responses being important measures of response. While PSA and radiographic responses are important, the ultimate objective is to improve survival with treatment. In my clinical practice, I have had several patients continue to respond to ZYTIGA® combination therapy for several years.

219. Doctors prescribe ZYTIGA® therapy for mCRPC patients because of the observed enhanced survival benefit of the combination of abiraterone acetate and prednisone in mCRPC patients. (Ex. 1034 (de Bono 2011); Ex. 1009 (Ryan 2013); Ex. 2071 (Ryan 2015). In fact, this is why I prescribe ZYTIGA® therapy for my mCRPC patients. The survival advantage provided by treatment with abiraterone acetate plus prednisone coupled with extensive testing of the combination during development, far out-weighs the risks of prednisone's side-

effects. Therefore, in my opinion, the therapeutic effect of prednisone in combination with abiraterone acetate in the treatment of prostate cancer contributes significantly to the success of ZYTIGA®.

C. Long Felt But Unsolved Need

220. Prior to the discovery of the inventions claimed in the '438 Patent, which is embodied in the FDA-approved method of using ZYTIGA®, the prognosis for men with mCRPC was dismal, with a diagnosis typically leading to death within approximately 12 months. No comparable treatment existed that could extend the life of mCRPC patients. Only docetaxel-based chemotherapy, which worked by a completely different mechanism and required intravenous administration, had been shown to provide a modest survival benefit in mCRPC patients. As a result, mCRPC patients were left with few treatment options, and there was an urgent need for new agents that would improve survival. (Ex. 1023 Attard (2005) at 1241).

D. Skepticism and Failure of Others

221. Cancer drugs typically have a lower than average success rate in Phase III trials than other therapeutic areas. (Ex. 2072 (Booth) at 609) ("[E]arly development trials do not seem to be very predictive of success rates for later development . . . . Phase II trials in oncology do not show significant predictability for Phase III outcomes."). Clinical trials of mCRPC are no exception. As

discussed above, as of August 2006, a myriad of potential therapies were being attempted in the search for an improved treatment for mCRPC. (*See supra* at ¶¶ 60-61). The majority of these failed to demonstrate efficacy, despite showing promise in early stage trials, and prior art was littered with examples of mCRPC treatments that failed to demonstrate efficacy in Phase II and III clinical trials.

1. The O'Donnell Studies

222. In 1996, Boehringer Ingelheim ("Boehringer"), licensed the secondary hormonal agent abiraterone acetate from BTG International Ltd. ("BTG") with the goal of developing an alternative first-line hormonal therapy. (Ex. 2013). Boehringer conducted three separate Phase 1 (toxicity) studies in which abiraterone acetate was administered as a monotherapy to investigate its ability to suppress testosterone in castrate in non-castrate males, which are reported in O'Donnell. These trials did not establish abiraterone acetate's clinical efficacy and in 1999, Boehringer halted the entire development program. (Ex. 2028 at ¶ 7).

223. It is my understanding that later attempts to find an alternative partner for developing abiraterone acetate proved difficult. (*Id.*). Even attempts to publish the O'Donnell manuscript were met with skepticism in the field and the manuscript was rejected by various medical journals, including *Clinical Cancer Research*, which received reviewer comments stating that there existed "little persuasive data" that residual androgens are important in stimulating prostate cancer growth.

(*Id.* at ¶ 8; Ex. 2030). In fact, no clinical data concerning abiraterone acetate was ever reported until O'Donnell published in 2004, years after the data was collected.

224. In my view, the fact that research with abiraterone acetate was taken up by the inventors in view of skepticism that compounds using its mechanism of action would even work to reduce prostate cancer growth proves that their work was counter-intuitive, and their efforts anything but obvious.

2. Other Failed Phase III Clinical Trials

225. Set forth below are specific examples of proposed mCRPC therapies that failed in Phase III clinical trials:

- Ketoconazole — Phase III clinical trial of antiandrogen withdrawal alone or in combination with ketoconazole failed to show any difference in survival. (Ex. 2063 (Small) at *Abstract*, 1031).

- Ketoconazole — Phase II clinical trial of ketoconazole and ketoconazole/doxorubicin discontinued due to "intolerable side effects," because "[e]ach of the regimens is toxic" and because "neither of these regimens is sufficiently promising to justify phase 3 evaluation." (Ex. 2064 (Millikan) at Abstract, 114-115).

- Galeterone (TOK-001) — Phase III clinical trial failed. (Ex. 2073 (Tokai July 26, 2016 Press Release).

- Tasquinimod (ABR-215050) — Oral immunotherapy; Phase III clinical trial failed to show any improvement in overall survival. (Ex. 2074 (Active/Ipsen April 16, 2015 Press Release)).

- Orteronel (TAK-700) — 17,20-lyase inhibitor; two Phase III clinical trials failed to show any improvement in overall survival. (Ex. 2075 (Takeda June 19, 2014 Press Release)).

- Sunitinib — inhibitor of anti-VEGF, anti-PDGF, and inhibitor of tyrosine kinase receptor; Phase III clinical trial terminated early after it failed to show any improvement in overall survival. (Ex. 2076 (Michaelson (2014)).

- Custirsen (OGX-011) — Phase III clinical trial failed to show improvement in overall survival. (Ex. 2077 (OncoGenex (April 28, 2014) Press Release).

- Yervoy® (ipilimumab) — recombinant human monoclonal antibody; Phase III clinical trial failed to show improvement in overall survival. (Ex. 2078 (BMS Sept. 12, 2013 Press Release)).

- Atrasentan — selective endothelial-A receptor antagonist; Phase III clinical trials failed to delay disease progression or show increase in overall survival. (Ex. 2079 (Carducci); Ex. 2080 (Antonarakis)).

- Avastin® (bevacizumab) — endothelial growth factor-specific angiogenesis inhibitor; Phase III clinical trial failed to show increase in overall survival. (Ex. 2081 (Roche March 12, 2010 Press Release)).

- GVAX — immunotherapy; Phase III clinical trial failed to show effect on survival or showed toxicity. (Ex. 2082 (Mulcahy (2008)).

- Calcitriol (DN-101) (Asentar™) — Phase III trial failed to improve overall survival. (Ex. 2117 (Williams (2009) at 1593; Ex. 2083 (Novacea Form 8-K) at 2.

- MLN-2704 — conjugate of the anti-PSMA monoclonal antibody; development discontinued for undisclosed reasons. (Ex. 2084 (ImmunoGen, Inc. Form 8-K, Item 8.01) at 2); Ex. 2116 (Williams (2008) at 279.).

- Epothilone-D (KOS-862) — tubulin antagonist; failed Phase III clinical trial after primary efficacy endpoints were not met. (Ex. 2116 (Williams (2008) at 1815).

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

Executed on March 8, 2017 in Los Angeles, CA, USA

By: _____
Matthew B. Rettig, M.D.

APPENDIX A

ACI – What is Prostate Cancer?

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Declaration of Ian Judson

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