UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.

Petitioner

v.

ASTRAZENECA AB

Patent Owner

Case IPR2016-01325

U.S. Patent 8,329,680 B2

DECLARATION OF JOHN F. R. ROBERTSON, M.D. IN SUPPORT OF PATENT OWNER'S PRELIMINARY RESPONSE

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I, John F. R. Robertson, M.D., do hereby make the following declaration:

I) INTRODUCTION

1. I am over the age of eighteen and competent to make this declaration.

2. I have been retained as an expert witness on behalf of AstraZeneca AB for the above-captioned *inter partes* review (IPR). I am being compensated at my customary rate of £600 per hour for my consultation in connection with this matter. My compensation is in no way dependent on the outcome of my analysis or opinions rendered in this matter. A copy of my curriculum vitae, which includes my academic background, work experience, and select publications and presentations, is attached to this declaration as Exhibit A.

II) QUALIFICATIONS AND EXPERIENCE

3. My name is John Robertson, M.D. I am a physician specializing in breast cancer and surgery, and I have Specialist Accreditation in General Surgery. I trained and have worked as a general surgeon, focusing primarily on breast cancer, for thirty-five years, through which I have acquired extensive clinical experience in breast disease. Since August 1998, I have been Professor of Surgery at the University of Nottingham, initially based at the City Hospital, Nottingham (1988 - 2011) and then based at the Royal Derby Hospital, Derby (2011 - present). Prior to that, since 1992, my appointments included Senior Lecturer and Reader in Surgery, both based at the City Hospital, Nottingham. I

have clinical experience across the continuum of breast care, from preventive care for high risk patients and routine screening, to diagnosis and treatment of primary breast cancer, to diagnosis and treatment of locally advanced and metastatic disease, to palliative care.

4. I received my M.B. Ch.B. (Bachelor of Medicine, Bachelor of Surgery), B.Sc. (Bachelor of Science) and M.D. (in the UK, a postgraduate research degree in medicine) all from the University of Glasgow. I also was awarded F.R.C.S. (Fellowship of the Royal College of Surgeons) by the Royal College of Physicians and Surgeons of Glasgow.

5. My knowledge concerning the treatment of breast cancer, more specifically hormonal dependent breast cancer, and the use of hormone (*i.e.*, endocrine) therapies has been gained through my training and personal and professional experiences. More specifically, these experiences include my own medical practice over thirty-five years, research that I have conducted (both laboratory research and clinical trial research), consultancy positions I have held, and advisory boards and committees that I have served on or been a member of. In my medical practice, I have gained extensive experience over the last thirty-five years with every class of approved endocrine agent used to treat hormonal dependent breast cancer. Over my career, I have treated thousands of women with hormone dependent breast cancer.

6. In terms of research, I have been involved in both laboratory research and clinical trials of all major classes of new endocrine therapies in hormonal dependent breast cancer over thirty years. I have consulted for and served on or chaired advisory boards to major pharmaceutical companies researching and developing drugs for hormonal dependent breast cancer.

7. One of my major clinical and laboratory research interests is breast cancer, particularly hormonal dependent, or hormone receptor positive, breast cancer and the role of endocrine therapy. I have also had a focus on advanced disease—both locally advanced and metastatic breast cancer. As a surgical oncologist with both a major clinical and laboratory interest in endocrine and growth factor therapies, I find myself in a central position providing a link between surgical and non-surgical (clinical and medical) oncologists, which ensures seamless continuity of care for patients and a rich base from which clinical and laboratory research can proceed. At the University of Nottingham, my group's interest in systemic therapies has placed it at the vanguard of surgical units performing pre-surgical ('window of opportunity') studies which allows us to combine our skill sets in surgery and systemic therapies into a translational research program investigating biological changes in breast cancers, which matches our therapeutic clinical trials in advanced disease. I am currently one of the three Chief Investigators on the largest trial of peri-operative endocrine

therapy in the world (the POETIC trial). I have been Chief Investigator, or local Principal Investigator, in a large number of multicenter trials for new drugs produced by a variety of pharmaceutical companies including AstraZeneca, Novartis, Amgen, GlaxoSmithKline, Schering, and Bayer.

8. I have published extensively in the field of cancer, principally, although not exclusively, on topics related to cancer of the breast with a particular focus on hormonal dependent breast cancer and endocrine therapies. I currently have over 300 peer-reviewed publications. I have also published book chapters on the treatment of breast cancer and a book titled, Endocrine Therapy of Breast Cancer.

9. I have attended, over the last thirty years, a large number of professional oncology conferences, with a primary focus on breast cancer. I have presented at a number of professional conferences regarding my research related to breast cancer. In addition to presenting laboratory and clinical trial research, I have given invited lectures at both national and international conferences. I am frequently invited to lecture at international cancer meetings. Between 2009 and September 2016, I gave invited lectures at fifty-five international cancer meetings, often giving multiple lectures at a single meeting. One of the major topics of invited lectures has been the treatment of breast cancer and the use of hormone therapies, otherwise known as endocrine therapies.

10. I am a member of several learned societies, including: the Society of Academic and Research Surgery, the British Association of Surgical Oncology, the Association of Breast Surgery, and the British Association of Cancer Research. I am also a member, or have been a member, of several scientific committees as well as committees affiliated with universities and health care centers. I am the Editor-in-Chief of the journal, Breast Cancer Online.

11. I have extensive teaching experience, including in the subject of breast cancer. In addition, I have supervised a number of under- and post-graduate medical trainees and non-clinical scientists, including nearly twenty such physicians and students during the past five years.

12. I have significant experience in the areas of breast cancer diagnosis and treatment, breast cancer clinical trial research, hormonal dependent, or hormone receptor positive, breast cancer, and hormonal therapies. Therefore, I believe that I am qualified to render the opinions set forth in this report.

13. In the past four years, I have testified in the following litigation: *AstraZeneca Pharmaceuticals LP v. Sagent Pharmaceuticals, Inc.*, No. 14-cv-03547-RMB-KMW (D.N.J.).

III) MY UNDERSTANDING OF THE PROCEEDING

14. I have been informed that this proceeding is an *inter partes* review ("IPR") before the Patent Trial and Appeal Board of the United States Patent and

Trademark Office ("the Board"). I have been informed that an IPR is a proceeding to review the patentability of one or more issued claims in a United States patent on the grounds that the patent is the same as or rendered obvious in view of the prior art.

15. I have been informed that Mylan Pharmaceuticals Inc. filed a Petition requesting IPR ("Petition") of U.S. Patent No. 8,329,680 (the '680 Patent"), which issued to John R. Evans and Rosalind U. Grundy on December 11, 2012 and is assigned to AstraZeneca AB. I have reviewed the Petition, and understand that it alleges that claims 1-20 of the '680 Patent are unpatentable over McLeskey (Ex. 1005) and, alternatively, over the combination of Howell 1996 (Ex. 1006) with McLeskey (Ex. 1005).

IV) MY OPINIONS AND THEIR BASES

16. I have been asked to give my opinion on whether or not a person of ordinary skill in the art ("POSA") would understand claims 1-20 of the '680 Patent to be rendered obvious by: (1) McLeskey (Ex. 1005); or (2) the combination of Howell 1996 (Ex. 1006) with McLeskey (Ex. 1005).

17. As part of this opinion, I considered the level of ordinary skill in the art around January 2000, which represents the filing date of GB 0000313, to which the '680 Patent claims priority.

V) DOCUMENTS CONSIDERED

18. The materials that I have considered, in addition to the exhibits to the Petition, are those cited herein (which are also listed in Exhibit B). My opinions as stated in this Declaration are based on the understanding of a POSA in the art as defined below.

VI) THE '680 PATENT CLAIMS

19. I have been informed that the priority date of the '680 Patent was January 10, 2000.

20. Independent claim 1 of the '680 Patent is provided below.

> 1. A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising administering intramuscularly to a human in need of such treatment a formulation comprising:
>
> about 50 $mgml^{-1}$ of fulvestrant;
>
> about 10% w/v of ethanol;
>
> about 10% w/v of benzyl alcohol;
>
> about 15% w/v of benzyl benzoate; and
>
> a sufficient amount of castor oil vehicle;
>
> wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for

at least four weeks.

21. Dependent claims limit claim 1 to a method: wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$ (claim 2); wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer (claims 3 and 6); wherein the method comprises administering intramuscularly to a human in need of such treatment 5 mL of the formulation (claims 4 and 7); wherein the method further comprises once monthly administration of the formulation (claims 5 and 8); wherein the formulation is administered in a divided dose (claims 17 and 18).

22. Independent claim 9 is provided below.

> 9. A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising administering intramuscularly to a human in need of such treatment a formulation consisting essentially of:
>
> about 50 $mgml^{-1}$ of fulvestrant;
>
> about 10% w/v of ethanol;
>
> about 10% w/v of benzyl alcohol;
>
> about 15% w/v of benzyl benzoate; and
>
> wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for

at least four weeks.

23. Dependent claims limit claim 9 to a method: wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$ (claim 10); wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer (claims 11 and 14); wherein the method comprises administering intramuscularly to a human in need of such treatment 5 mL of the formulation (claims 12 and 15); wherein the method further comprises once monthly administration of the formulation (claims 13 and 16); wherein the formulation is administered in a divided dose (claims 19 and 20).

VII) PERSON OF ORDINARY SKILL IN THE ART

24. I have been asked to provide my opinion on the novelty and obviousness of the asserted claims, from the perspective of a person of ordinary skill in the relevant art. The skilled person with respect to the '680 Patent is a person having a bachelor's or advanced degree in a discipline such as pharmacy, pharmaceutical sciences, endocrinology, medicine or related disciplines, and having at least two years of practical experience in drug development and/or drug delivery, or the clinical treatment of hormone dependent diseases of the breast and reproductive tract. Because the drug discovery and development process is complicated and multidisciplinary, it would require a team of individuals including, at least, medical doctors, pharmacokineticists, and formulators.

25. As considered from the perspective of the medical doctor member of that team, the invention of the '680 Patent is novel, and not obvious, for the following reasons.

VIII) LEGAL PRINCIPLES

26. I am not a lawyer, and I have relied on the explanations of counsel for an understanding of certain principles of U.S. patent law that govern the determination of patentability. The discussion set forth below regarding the law of obviousness is intended to be illustrative of the legal principles I considered while preparing my report, and not an exhaustive list.

27. I am informed by counsel that there is no presumption of validity. Rather, Mylan must show unpatentability by a preponderance of the evidence, and preponderance of the evidence means "more probable than not." I understand that to institute an *inter partes* review Mylan must show that there is a reasonable likelihood that it would prevail in an *inter partes* review.

28. I am informed by counsel that for a patent claim to be invalid as anticipated by a prior art reference, that reference must disclose every limitation of the claim. Thus, if the inventions of a patent claim were already disclosed, in their entirety, by a prior art reference, that claim is anticipated and not novel.

29. I am informed by counsel that for an invention to be obvious, the patent statute requires that the differences between the invention and the prior art

be 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 to which such subject matter pertains."

30. I understand that the obviousness evaluation must be from the perspective of the time the invention was made. The obviousness inquiry must guard against slipping into use of hindsight.

31. I understand that even in circumstances where each component of an invention can be found in the prior art, there must have been an apparent reason to combine the known elements in the fashion claimed by the patent at issue. For an invention to be found obvious, to protect against the distortion caused by hindsight bias, there must be a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

32. For the method of treatment to be obvious, it must have been among a finite number of identified, predictable solutions to the problems at hand.

33. For the reasons explained below, in my opinion, Mylan has not shown that there is a reasonable likelihood that it would prevail in an *inter partes* review of claims 1-20 of the '680 patent.

IX) CLAIM CONSTRUCTION

34. All of the claims of the '680 Patent are expressly directed to methods

of treatment. The methods of treatment include choice of an active ingredient, a method of administration (*i.e.*, a combination of excipients and active injected intramuscularly), and the amount of the active to be delivered to the blood in a sustained release fashion to treat hormonal dependent disease of the breast and reproductive tract.

35. A medical doctor would understand the term "hormonal dependent benign or malignant disease of the breast or reproductive tract . . . [in] a human" in independent claims 1 and 9 of the '680 Patent to have its plain and ordinary meaning. The plain meaning of this term indicates to a medical doctor that the method of treatment may be used to treat hormonal dependent cancerous and non-cancerous diseases of the breast or reproductive system, such as breast cancer or endometriosis, in pre- and post-menopausal women and breast cancer or gynaecomastia in men.

36. A medical doctor would understand that the blood plasma level limitations of the '680 Patent claims are indeed limitations of the claims and should be given their plain and ordinary meaning. These limitations are in claims 1 and 9: "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks" and in the claims which depend on them: "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$." A clinician would

understand these limitations to mean that the specified blood plasma fulvestrant concentrations of at least 2.5 $ngml^{-1}$ or 8.5 $ngml^{-1}$ are achieved and maintained for the specified amount of time. The plain meaning of the words "achieves" and "at least" indicate to the clinician that the patient's blood plasma level must remain at or above the specified concentrations for the entire specified time period.

37. Dr. Oleksowicz argues that the blood plasma levels "simply express[] the intended result of a process step positively recited" and inform that "if the as-claimed method of treatment is followed, the specified therapeutic plasma levels will be achieved." Ex. 1004 at ¶¶ 190-191, 223-224. In my opinion, this cannot be so because, from a clinician's perspective, these limitations give meaning to and provide defining characteristics of the method of treatment.

38. The blood plasma levels achieved and maintained are different for different claims. These limitations go to the dose and the dosing frequency of the method of treatment if it is to achieve a therapeutic outcome. Dose and dosing frequency are pivotal aspects of a method of treatment: they themselves are not included within the claims since what is even more critical in attaining a therapeutic outcome, and ultimately decides dose and dose schedule, is that the drug fulvestrant is delivered in the blood to the tumor at the specified blood plasma concentration for the specified duration. *See, e.g.*, Ex. 2014 (Pritchard 1997) at 13 ("The endocrine effects of tamoxifen are complex and seem dependent on species,

age, duration, and dose of tamoxifen given, menopausal status, and target organ."). Furthermore, as will be detailed below the different blood plasma concentrations lead to different therapeutic outcomes which highlight that the blood plasma limitations give meaning to and provide defining characteristics of the method of treatment.

39. Indeed, clinical studies demonstrated the therapeutic importance of the different blood plasma level limitations of the claims. I was a member of the team that conducted a translational clinical study investigating the 50 mg, 125 mg, and 250 mg doses of Faslodex® (fulvestrant) intramuscular injection as well as therapeutic clinical studies investigating 125 mg and 250 mg doses of Faslodex® (fulvestrant) intramuscular injection. Exs. 2028 (Howell 2002), 2029 (Osborne 2002), 2030 (Robertson Cancer Res. 2001), 2031 (Robertson Clin. Ther. 2003). The results of the clinical studies, published in 2002, demonstrated that the 125 mg dose did not achieve the desired therapeutic result and was therefore deemed not effective to treat hormonal dependent breast cancer. *Id.* The translational study, published in 2001, indicated that compared to the 250 mg dose the 50 mg and 125 mg doses appeared not as effective in decreasing estrogen receptor, progesterone receptor or Ki67 expression in tumors and at the same time achieved lower blood concentrations throughout the 4 week period. And, in fact, later studies showed that the 500 mg dose had improved efficacy even over the 250 mg dose (Ex. 2004

(Di Leo 2010); Ex. 2005 (Di Leo 2014)) and this was explicitly linked to the blood levels achieved by the 500 mg dose (Ex. 2006 (FINDER 1); Ex. 2007 (FINDER 2)). This demonstrates the criticality of the blood plasma level limitations of the claims.

X) STATE OF THE RELEVANT ART

A) Problem To Be Solved

40. Breast cancer was a problem at the time of the invention. Approximately 184,200 people in the United States were expected to be diagnosed with breast cancer in 2000, with over 41,000 deaths expected from the disease. Ex. 2008 (Greenlee) at 6-7. At the time of the invention, a variety of treatments existed for patients with breast cancer, one of which was endocrine therapies. Such therapies seek to alter hormone levels in a patient and/or the hormone receptor levels in the tumor to influence the progression of hormonal dependent breast cancer. Breast cancer is divided into hormone dependent and hormone independent subtypes. Approximately 46-77 percent of cases of breast cancer were considered hormone dependent. Ex. 2009 (Robertson 1996) at 1. The remaining one-third of breast cancer cases are hormone independent. This classification of breast cancer as hormone independent and hormone dependent is important because it guides the clinicians as to which type of treatment may be appropriate for a particular patient.

41. Dr. Oleksowicz states that "[h]ormonal-dependent breast cancer in

women was known to correlate with three hormone receptors: estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2)." Ex. 1004 at ¶ 37. Estrogen and progesterone receptors are hormone receptors. Dr. Oleksowicz misclassifies HER2 as a hormone receptor, for as its full name implies, it is in fact a growth factor receptor. As such, hormone receptors (ER and PGR) are used to define whether tumors are hormone dependent or independent. HER2 would be used to select patients for anti-growth factor therapy targeted at HER2 (*e.g.*, Herceptin®).

42. Of the endocrine therapies available prior to the invention of the '680 Patent, tamoxifen ("Nolvadex®") was "the most important hormonal antitumor agent for breast cancer." Ex. 2010 (Fornier) at 4; Ex. 2011 (Jordan Supp. 1995) at 1 ("Tamoxifen [] is the endocrine therapy of choice for selected patients with all stages of breast cancer."). Indeed, tamoxifen was "the most widely used first-line hormonal agent in patients with metastatic breast cancer." Ex. 2012 (Hortobagyi Cancer Investigation 1998) at 5. "Tamoxifen is a synthetic antiestrogen that blocks estrogen binding to the estrogen receptor (ER)." Ex. 2010 (Fornier) at 4.

43. Tamoxifen was known to be a partial agonist/antagonist. It blocked estrogen from fueling breast cancer tumors in breast tissue. But in other tissues like bone and the heart it acted like estrogen, providing beneficial protection. Ex. 1018 (Osborne 1995) at 5. Other references similarly described the importance

and benefits of tamoxifen's partial agonist/antagonist properties. Ex. 2022 (Minton) at 1; Ex. 2023 (Grese 1998) at 1-2. Tamoxifen was available as a once a day oral pill.

44. The success of tamoxifen led to attempts to improve the less desirable aspects of the drug. A significant clinical problem was that tamoxifen treatment eventually resulted in tumor resistance. Ex. 2010 (Fornier) at 4 ("Unfortunately, breast cancer in most patients will eventually become resistant to tamoxifen."). In other words, "most tumours that respond [to tamoxifen] eventually develop acquired resistance and start to regrow." Ex. 2013 (Johnston 1997) at 1.

45. Thus, prior to 2000, there was a need for (1) improved treatments for hormone dependent breast cancer, and (2) improved treatment options for patients following tamoxifen failure. Ex. 2014 (Pritchard 1997); Ex. 2015 (Buzdar Clin. Oncol. 1998); Ex. 2016 (Buzdar Clin. Cancer Res. 1998); Ex. 2013 (Johnston 1997); Ex. 2017 (Jordan 1995); Ex. 2018 (Morrow); Ex. 2019 (Wiebe); Ex. 2020 (Jordan Supp. 1992); Ex. 2021 (Jordan 1992). Metastatic breast cancer is an incurable condition so an endocrine therapy that could extend a woman's life and/or give her a better quality of life was desired.

46. Any treatment would have to be either more effective or at least as effective but safer than tamoxifen. In addition, it should be as convenient, *i.e.*, a once a day pill. Indeed, physicians thought that patients would not accept any

treatment but a once a day pill. Ex. 2020 (Jordan Supp. 1992) at 4 ("An orally active agent should be an essential component of any strategy to introduce a new antiestrogen. Oral tamoxifen is so well tolerated that patients would be reluctant to consider injections or sustained-release implants as an alternative.").

47. Within the endocrine therapies category, the prior art taught several different approaches, such as "improved" tamoxifens (other selective estrogen receptor modulators (SERMs)), aromatase inhibitors (AIs), and oral pure antiestrogens. Other approaches being used were antiprogestins and high dose estrogens, the latter which included approved and marketed products at the time.

48. In my view, Dr. Oleksowicz's analysis of endocrine therapy is incomplete (Ex. 1004 at ¶¶ 41-45), as she ignores whole classes of promising endocrine therapies, *e.g.*, antiprogestins, progestins and high dose estrogens. Furthermore, she fails to describe the important advantages of the SERMs currently used at the time (*e.g.*, bone and cardiovascular effects) but focuses solely on one *uncommon* negative effect of tamoxifen (uterine cancer). She also fails to discuss the extensive research that was ongoing to assess new "designer" SERMs, which were being developed to optimize the beneficial agonistic properties of SERMs while minimizing potential harmful agonistic properties. Additionally, Dr. Oleksowicz fails to recognize that, even beyond the designer SERMs, the aromatase inhibitors had become the new and preferred focus for pharmaceutical companies

and clinical researchers seeking new and more effective endocrine agents, including the second and third generation aromatase inhibitors that were being developed for various clinical indications in breast cancer. Finally, in terms of pure antiestrogens, she does not acknowledge the other pure antiestrogens being developed immediately prior to 2000, of which one in particular, EM-800, was more potent, orally active, had phase II clinical data, and had started phase III clinical trials. For the reasons described above and below, a skilled artisan would not have begun with fulvestrant as the active ingredient, nor would a skilled artisan have expected such an approach to succeed.

B) The Prior Art Taught and Provided a Promising Scientific Rationale and Experimental Candidates for Many Different Systemic Therapy Approaches to Treating Breast Cancer

1) Selective Estrogen Receptor Modulators (SERMs)

49. Given the success of tamoxifen and the benefits of its mixed agonist/antagonist activity, one of the promising areas was the search for a new tamoxifen with a better balance of activities. As of the date of the invention, several SERMs had already received FDA approval, opportunities existed to improve the most widely used SERM, tamoxifen, and many promising SERMs were in development.

50. Contrary to Dr. Oleksowicz's assertion that some of tamoxifen's agonist activity that was not beneficial (the rare instances of endometrial cancer)

pointed to pure estrogen antagonists, Ex. 1004 at ¶ 49, in reality, at the time of the invention, many scientists and pharmaceutical companies were attempting to develop better SERMs by seeking a superior balance between antiestrogen activity and estrogen agonist activity, instead of entirely eliminating agonist activity. The prior art explained exactly that: "[t]he finding of endometrial cancer resulting from tamoxifen treatment has led researchers to investigate new agents that retain favorable estrogenic properties in specific tissues and display antiestrogen activity on the endometrium. Such research has generated the concept of selective estrogen receptor modulators (SERMs) that mediate either estrogen agonist or estrogen antagonist effects in different tissues." Ex. 2022 (Minton) at 1.

51. In fact, the focus on improving the agonist-antagonist balance of tamoxifen led to an "explosion of research to understand the molecular basis for this specificity and a race to develop these 'designer estrogens' or Selective Estrogen Receptor Modulators (SERMs) as pharmaceutical products." Ex. 2023 (Grese 1998) at 2.

52. As of the date of the invention, other SERMs that had received FDA approval included toremifene, which was found to be as efficacious as tamoxifen in the first-line setting (Ex. 2022 (Minton) at 2), and raloxifene for osteoporosis (Ex. 2024 (Hortobagyi New Eng. J. Med. 1998) at 9). Many promising SERMs were also known to be in clinical development at the time including idoxifene (in a phase

I clinical trial "was well tolerated with only mild toxicities, and the patients had a partial response rate and stable response rate of 14% and 29%, respectively, ranging from 1.4 to 14 months"), droloxifene (multiple phase II trials had been reported, with the largest showing "a 30% response in the 20-mg arm compared to a 47% response in the 40-mg arm and a 44% response in the 100-mg arm" with side effects "similar to that of tamoxifen"), TAT-59 (in a phase I clinical trial "[t]he total response rate was 30% in the TAT-59 arm compared to 26.5% in the tamoxifen arm"), arzoxifene (reported to be "a SERM with improved *in vivo* potency as an oral estrogen antagonist, which maintains tissue-specific estrogen agonist effects on serum cholesterol and bone mineral density at doses as low as 0.01 mg/kg"), CP-336,156 (identified as "a potent tissue selective estrogen agonist"), and LY326315 (known to possess "a fully differentiated agonist/antagonist profile on reproductive vs. non-reproductive tissue"). Ex. 2022 (Minton) at 2; Ex. 2023 (Grese 1998) at 11-12.

2) Aromatase Inhibitors (AIs)

53. The most promising endocrine therapies at the time of the invention were aromatase inhibitors. Indeed, this class was the primary focus of many researchers at the time aiming to solve the problem of tamoxifen resistance. Unlike fulvestrant, tamoxifen, and the newer SERMs, aromatase inhibitors had a very different and known mechanism of action. Rather than targeting the estrogen

receptor (like all the SERMs and fulvestrant), the aromatase inhibitors targeted the aromatase enzyme[1] and inhibited the formation of estrogen, the ligand for the estrogen receptor. This meant that aromatase inhibitors were less likely than other SERMs and fulvestrant to be "cross-resistant" to tamoxifen. "Cross-resistance" means that a drug's efficacy is significantly reduced when it is administered to a patient following progression on a different drug with a similar mechanism of action. In particular, an advantage of aromatase inhibitors noted at the time was that they are "effective therapy in patients with breast cancer even after they relapse from responses to antiestrogen or progestin (medroxyprogesterone acetate or megestrol acetate) therapy." Ex. 2025 (Masamura 1994) at 2 (emphasis added).

54. At the time of the invention, anastrozole (Arimidex®) and letrozole (Femara®) had received FDA approval in the second-line endocrine therapy setting. Ex. 2022 (Minton) at 3. In late 1999, exemestane received similar FDA approval as Aromasin®.

55. AIs that had been in development prior to the invention included vorozole ("[p]otent aromatase inhibition, few side effects, and possibility of

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[1] Aromatase is the enzyme that catalyzes the rate-limiting step in the formation of estrogen. Ex. 2026 (Kelloff 1998) at 1. Clinical studies had shown that "aromatase inhibitors cause tumor regression in postmenopausal breast cancer patients." Ex. 2026 (Kelloff 1998) at 2.

influencing estradiol levels in premenopausal women are of interest for chemoprevention"), formestane ("approved in Europe for the treatment of metastatic breast cancer in women who have failed tamoxifen therapy . . . has been shown to have high response rates"), fadrozole (CGS 16949A) ("studies demonstrated that fadrozole is 500-fold more potent than aminoglutethimide"), ORG 33201 ("[a]lthough less potent than fadrozole in the model systems examined, it was more selective and did not demonstrate any additional unwanted hormonal activity"), and CGP 47645 ("a fluorinated derivative of letrozole, which is equipotent with letrozole toward aromatase *in vitro* but is 10 times more active *in vivo*"). Ex. 2022 (Minton) at 4; Ex. 2025 (Masamura 1994) at 4; Ex. 2026 (Kelloff 1998) at 5, 9.

56. At the time of the invention, the skilled artisan would have focused on AIs, as demonstrated by the prior AIs that received FDA approval, the possibility of improving on existing endocrine therapies with newer AIs, and the reports of promising AIs in development. Further, the known mechanism of action of AIs was important for researchers because researchers are always looking for the most promising path; proven mechanisms are much less risky than unproven mechanisms.

3) Pure Antiestrogens

57. Dr. Oleksowicz argues that "researchers were aware that a pure anti-

estrogen might provide anti-tumor activity superior to tamoxifen in certain human females with breast cancer." Ex. 1004 at ¶ 111. The key word there is "might." No pure antiestrogen had been approved at the time of the invention. At the time of the invention, few pure antiestrogens were even in development and, as noted below, fulvestrant was not the most promising candidate.

58. Researchers hoping to find a treatment for tamoxifen-resistant patients would have been hesitant of approaches that focused on the estrogen receptor, as tamoxifen also operated on the estrogen receptor and usually resulted in tumor resistance. Ex. 1018 (Osborne 1995) at 1 ("Most tumors eventually became resistant to [fulvestrant] and grew independently of estrogen."). Researchers also highlighted a potential risk of pure antiestrogens -- cross-resistance with tamoxifen --"[o]n the basis of our data, we would predict that most patients with ICI 182,780-resistant tumors, would not respond well to subsequent treatment with tamoxifen." *Id.* at 5. In this circumstance, the value of using sequential endocrine agents would be negated. On the other hand, aromatase inhibitors exhibited alternative mechanisms of action that were believed to offer potential solutions to tamoxifen resistance.

59. Moreover, in terms of side effects, it was feared that pure antiestrogens would have deleterious effects on the bone and heart as opposed to the beneficial effects on bone and the heart provided by tamoxifen and other SERMs. Ex. 2027

(Dukes 1994) at 5 ("[A] possible undesirable consequence of pure antioestrogen therapy is an adverse effect on bone mineral metabolism leading to induction or exacerbation of osteoporosis."); Ex. 1018 (Osborne 1995) at 5 ("The estrogenic properties of tamoxifen in bone and on blood lipids may help to reduce bone loss and prevent cardiovascular disease . . . . The effect of [fulvestrant] on these parameters is not yet known, but it might be deleterious given its lack of estrogenic qualities."); Ex. 2023 (Grese 1998) at 4 ("For example, ICI 164,384 and ICI 182,780 exhibited no capacity for lowering serum cholesterol or sparing bone loss in the OVX rat model.").

60. Dr. Oleksowicz alleges that "[b]y the early 1990s, researchers were aware of the drawbacks to partial estrogen antagonists like tamoxifen . . . [and] recognized that a pure anti-estrogen, unlike tamoxifen, could provide '*complete* ablation of the estrogen-mediated tumor growth.'" Ex. 1004 at ¶ 111 (emphasis in original). But, in fact, the lack of precedent for successfully developing a pure antiestrogen, its unproven mechanism of action, and the potential disadvantages on bone and lipids would have discouraged a skilled artisan from taking a pure antiestrogen approach. This is reflected in the relatively few pure antiestrogens known in the art at the time of the invention.

61. But, even if a skilled artisan were interested in pure antiestrogens, such a person would have focused on the most potent pure antiestrogens and those that

could be administered orally. A number of them existed, including EM-652, EM-800, RU 58668, and ZM 189,154. Ex. 2022 (Minton) at 3; Ex. 2032 (Labrie 2004); Ex. 2034 (Labrie 1999); Ex. 2033 (Van de Velde); Ex. 2027 (Dukes 1994). For example, "EM-652 is the active metabolite of the prodrug EM-800 and is available in oral form." Ex. 2022 (Minton) at 3. EM-652 was reported to be "20 times more potent" than fulvestrant. Ex. 2022 (Minton) at 3. "EM-652 has the highest known affinity to the ER when studied in competition receptor assays in animal models." Ex. 2022 (Minton) at 3. Based on oral bioavailability and superior potency, a skilled artisan would have preferred the EM series of compounds over fulvestrant.

62. Additionally, "a small [] phase II trial investigating EM-800 in the metastatic breast cancer setting in women who had progressed on tamoxifen showed encouraging results and thus implie[d] a lack of cross-resistance with tamoxifen." Ex. 2022 (Minton) at 4. These encouraging results which were published in 1999 before the invention of the '680 Patent revealed EM-800 as a promising new agent, with 19 out of the 43 patients (44%) studied reporting positive responses to treatment. Ex. 2034 (Labrie 1999) at 26-28. Prior to 2000, this led to EM-800 being "studied in a large [phase III] trial comparing its efficacy to anastrozole in the second-line treatment setting of metastatic breast cancer" to demonstrate that EM-800 should become a standard of care. Ex. 2022 (Minton) at 4. On the other hand, Howell 1995 and Howell 1996 report a less potent estrogen

receptor antagonist being delivered in a parenteral formulation.

63. Even if a skilled artisan wanted to develop a pure antiestrogen at the time of the invention of the '680 Patent, such a person would have preferred compounds with oral bioavailability and/or improved potency compared to fulvestrant.

4) Other Endocrine Therapies

64. Progestins, anti-progestins, androgens and luteinizing hormone-releasing hormone agonists (LHRH agonists) were all additional approaches that had been attempted in clinical trials prior to the invention of the '680 Patent, which worked to impact the hormonal-dependent pathway. Each of those classes had individual agents described in the literature as having promise and each had the benefit of having a different mechanism of action than tamoxifen. An example of a progestin that had been developed includes megestrol acetate. Ex. 2035 (Hortobagyi 1998) at 2. Examples of anti-progestins in development at the time include onapristone, ORG 31710, and ORG 31806. Ex. 2036 (Robertson 1999); Ex. 2016 (Buzdar Clin. Cancer Res. 1998) at 7. Fluoxymesterone, a synthetic androgen, had been "used in patients with persistently hormone-responsive tumors as fourth-line therapy." Ex. 2035 (Hortobagyi 1998) at 3. Leuteinizing hormone-releasing hormone analogs such as goserelin had "proven to be of major efficacy in chemical gonadal ablation in both women and men." Ex. 2035 (Hortobagyi 1998)

at 2; Ex. 2037 (Hortobagyi 1997) at 1.

65. As described above, the skilled artisan at the time of the invention would have had numerous approaches to systemic endocrine therapies for breast cancer treatment, each with promising compounds.

C) Fulvestrant Was Less Promising Than The Other Available Endocrine Agents in 2000

66. In my opinion, at the time of the invention, the skilled artisan would not have been motivated to select fulvestrant to develop a treatment of hormonal dependent benign and malignant diseases of the breast and reproductive tract, including breast cancer, and would not have had a reasonable expectation of success in doing so.

67. In my view, fulvestrant was less promising as a potential treatment than other available endocine agents. Dr. Oleksowicz argues that "there was a motivation to develop novel endocrine therapies that worked as pure estrogen antagonists" and equates that argument for the class as a reason to select fulvestrant. Ex. 1004 at ¶¶ 49, 111-132. In my view, this misrepresents the state of the art in January 2000.

68. Of the more than 15 other endocrine agents available in 2000, fulvestrant was not the most promising. First, fulvestrant was from a new class that had many risks. While it was known to target the estrogen receptor, it had an unproven (and not fully understood) mechanism of action than the other endocrine

agents such as the aromatase inhibitors (*i.e.*, the most promising class at that time) and the designer SERMs, and activities within these other classes were already more advanced in their development at the time. Scientists did not expect that fulvestrant would be more effective than AIs or SERMs, even after the publication of Howell 1995. "It remains to be seen whether it will be more effective than other non-steroidal anti-oestrogens with less agonist activity than tamoxifen or toremifene, such as idoxifene. Our data suggest that it may not be substantially more effective in terms of response rate than aromatase inhibitors, with which it is conceptually similar in its pure deprivation of the oestrogenic signal." Ex. 2038 (Dowsett 1995) at 1.

69. Second, even within its class, fulvestrant was not the most attractive of the pure antiestrogens. For example, EM-800 was already in phase III trials, thought to be more potent than ICI 182,780, and had shown good activity in phase II trials. Additionally, the oral pure antiestrogen compounds, such as EM-800 or ZM 189,154, were more attractive options for both patients and physicians due to the issues that are associated with parenteral drug administration.

70. Thirdly, it was important that a new endocrine therapy was not associated with cross-resistance to subsequent endocrine therapies – indeed not being cross-resistant was one of the desired features for a new endocrine therapy. Osborne had raised this concern about cross-resistance with tamoxifen --"[o]n the

basis of our data, we would predict that most patients with ICI 182,780-resistant tumors, would not respond well to subsequent treatment with tamoxifen." Ex. 1018 at 5 . This was a concern that was further highlighted even after the small non-randomised study (n=19) by Howell 1996. In the small sub-group of responders from the Howell 1996 study all failed to show an objective response to subsequent third-line therapy with megestrol acetate. Ex. 2041 (Robertson 1997) at 3 ("[T]his early finding raises the hypothesis as to whether acquired resistance to [fulvestrant] may be equivalent to developing an endocrine resistant phenotype.").

71. Dr. Oleksowicz's declaration includes a section in which she makes claims regarding the clinical efficacy and safety of fulvestrant, which have no basis, are over-interpretations of available data, or statements about the potential and promise of the compound. Ex. 1004 at ¶¶ 125-132. Relying on this, I understand that Mylan is arguing that "fulvestrant was long known in the art to be an efficacious treatment for breast cancer," "[f]ulvestrant is a steroidal ERD that has, at least since the compound was patented in 1987, been known to be efficacious in the treatment of breast cancer," and "[t]he prior art long taught that fulvestrant was known to be effective to treat breast cancer in women, specifically, HD malignant breast cancer in women." Petition at 8-10, 22.

72. However, every reference that Dr. Oleksowicz cites uses language like "potential," "maybe," or "might" indicating at most a hope not an expectation and

certainly not "knowledge." Ex. 1013 (O'Regan 1998) at 1 ("ICI 182,780 ***may*** prove useful as an adjuvant agent in early stage endometrial cancer." (emphasis added)); Ex. 1008 (Wakeling 1991) at 7 ("The data available to date for ICI 182,780 presented here [] indicate that pure antiestrogens ***may*** find a valuable place in the treatment of breast cancer." (emphasis added)); Ex. 1026 (Dukes 1993) at 1 ("ICI 182,780 is a potent specific pure antioestrogen which ***may prove*** superior to conventional partial agonist antioestrogens in the treatment of breast cancer." (emphasis added)); Ex. 1028 (Wakeling 1993) at 8 ("If the greater efficacy of pure versus partial agonist antiestrogens against human breast cancer cell growth described above translates to the clinical setting, one ***might anticipate*** significant benefits in the rate and extent of tumor remission following pure antiestrogen therapy compared with other 'antiestrogenic' therapies." (emphasis added)). This does not demonstrate that fulvestrant's human clinical efficacy in breast cancer patients was "well known."

73. Additionally, Dr. Oleksowicz states "[t]hese trials [DeFriend 1994 and Howell 1995/1996] not only demonstrated fulvestrant's robust anti-tumor activity in tamoxifen-resistant female ER+ breast cancers, but also suggested that fulvestrant was potentially more efficacious than tamoxifen." Ex. 1004 at ¶ 127. This is contradicted by the references. No comparison is made of fulvestrant versus tamoxifen in either study; this statement by Dr. Oleksowicz therefore has no basis.

And, the claim that fulvestrant "demonstrated robust anti-tumor activity" in those two studies is an exaggeration of the results.

74. By the time of the invention, there had only been 19 highly selected patients ever treated in one small, non-randomized, phase II clinical study (Howell 1995/1996), which itself recognized the need for further clinical trials to assess the efficacy of fulvestrant. Ex. 1006 at 6 ("The lack of apparent adverse effects of ICI 182,780 seen in the present study would, ***if confirmed in future larger trials***, give the specific anti-oestrogen potential advantages over currently available second-line endocrine agents." (emphasis added)). Howell 1996 reported that 13 of 19 patients responded (69%): 7 "partial responders," whose tumors decreased in size; and 6 "no change" patients, whose tumors neither shrank nor grew but remained stable, which was considered by some researchers to be a clinically beneficial outcome. Howell 1996 also noted that up to one-third of responses could have been due tamoxifen withdrawal, *i.e.*, shrinkage of the cancer due to coming off tamoxifen and taking away the estrogen stimulation that is associated with tamoxifen. Ex. 1006 at 7 ("[W]e and others have demonstrated so-called withdrawal responses in breast cancer patients after stopping treatment with tamoxifen at the time of tumour progression, further suggesting tumour stimulation by tamoxifen as a possible cause of treatment failure . . . [I]n most studies withdrawal responses occur in only one-third or less of patients[.]"). Accordingly,

because all of the patients in Howell 1996 previously progressed while on tamoxifen, the skilled artisan would understand that up to one-third of the responses (2 of 7 partial responders; and 2 of 6 no change) may be attributed to tamoxifen withdrawal rather than treatment with fulvestrant. Thus, the actual number of patients whose tumors showed shrinkage based on treatment with fulvestrant may have been as low as 5 patients. Other researchers at the time explained that for this and other reasons the results in Howell "should be interpreted with care in relation to other published data." Ex. 2038 (Dowsett 1995) at 1.

75. The conclusion at the time was that fulvestrant at best had some promise, but no more than other agents, yet it also held significant disadvantages which pointed away from its development in favor of agents from other less risky classes or better pure antiestrogens like EM-800.

D) Fulvestrant Formulations, Schedule And Route Of Administration, Optimal Dose, Concentration, and Blood Plasma Levels Were Not Well-Known And Were Certainly Not "Established" In The Prior Art

76. Dr. Oleksowicz attempts to compartmentalize the claimed method of treatment into its individual parts, stating that "multiple preclinical and clinical publications demonstrated not only the clinical efficacy of fulvestrant in the setting of ER+ breast cancer, but also documented its route and schedule of administration, formulation, optimal dose, volume and concentration, and blood

plasma serum fulvestrant concentration levels." Ex. 1004 at ¶ 133. To pull each of these factors apart is to fundamentally misunderstand drug delivery. From a clinician's perspective, one cannot divorce any one of these factors from the others. Indeed, clinicians realize that these factors are inextricably intertwined—changing one can radically affect the others.

77. The sweeping generalizations of Dr. Oleksowicz's declaration oversimplify the interactions of formulation, dose, route of administration, and scheduling in terms of their impact on drug delivery and efficacy. Indeed, it is the importance of such interactions which requires the method of treatment of drugs (*i.e.*, formulation, dose, route of administration, and scheduling) to be clearly stated on a drug approved by regulatory authorities.

78. Regarding indication, despite referencing "multiple publications" reporting on human research with fulvestrant, Dr. Oleksowicz cites to two such studies, Howell 1995/1996 (both Howell references related to the same study of 19 patients) and DeFriend 1994. Ex. 1004 at ¶ 134. At the same time she ignores another publication relating to a study in humans. Ex. 2039 (Thomas). These three studies give no consistent data regarding formulation, dose, or delivery schedule. Thomas uses a short-acting fulvestrant formulation delivered as a 12 mg i.m. injection daily for 7 days (Ex. 2039 (Thomas)); DeFriend 1994 uses a short-acting propylene glycol fulvestrant formulation delivered as a 6 or 18 mg i.m.

injection daily for 7 days (Ex. 1027 (DeFriend 1994)); Howell 1995/1996 uses a long-acting castor oil-based fulvestrant formulation (with no further information regarding ingredients) delivered as a 250 mg i.m. injection every four weeks (Exs. 1006 (Howell 1996), 1012 (Howell 1995)). At most this could suggest daily use was the aim, like tamoxifen and the existing AIs.

79. Dr. Oleksowicz says that the preclinical and clinical publications documented "optimal dose." Ex. 1004 at ¶ 133. But these studies, which used diverse doses (6, 12, 18, and 250 mg) in very different ways, do not say that. Ex. 2039 (Thomas); Ex. 1027 (DeFriend 1994); Ex. 1006 (Howell 1996); Ex. 1012 (Howell 1995). Instead, the Howell study explicitly states that the dose used was not optimal. It says "there was evidence of drug accumulation after multiple dosing such that after 6 months treatment there was an 80% increase in mean end of month drug levels and a 50% increase in the AUC compared with data from 1 month. These data suggest that lower doses of the drug may be as effective in maintaining therapeutic serum drug levels, although further clinical studies are required to confirm this hypothesis." Ex. 1006 (Howell 1996) at 6. Therefore, again, Dr. Oleksowicz's statement is incorrect. In any event, the dose is inextricably intertwined with the method of administration and its duration. "Optimal dose" was unknown.

80. Regarding excipients and percent w/v concentrations, Dr. Oleksowicz

argues that the prior art showed "fulvestrant formulations in castor oil, often accompanied with benzyl benzoate and ethanol." Ex. 1004 at ¶ 135. This too is not true. Only the McLeskey reference mentioned those ingredients -- no other reference. And McLeskey called that a "treatment failure" (see below). Despite Dr. Oleksowicz's attempt to suggest otherwise, none of the references cited describe a successful fulvestrant formulation with castor oil, benzyl benzoate and ethanol either in preclinical or clinical studies. Instead, Dr. Oleksowicz's selection of McLeskey and her focus on that paper in her declaration is clearly a retrospective focus based on the patent claims.

81. From a clinician's perspective, route and schedule of administration are critical factors. The various papers cited by Dr. Oleksowicz describe subcutaneous administration, oral administration and intramuscular administration as options used in research, with dosing schedules from once a day to once a month. The "optimal" dosing regimen would be once a day orally like tamoxifen. This regimen is supported by the art generally. Ex. 2020 (Jordan Supp. 1992) at 4 ("An orally active agent should be an essential component of any strategy to introduce a new antiestrogen. Oral tamoxifen is so well tolerated that patients would be reluctant to consider injections or sustained-release implants as an alternative."). Most of the papers cited by Dr. Oleksowicz use subcutaneous administration daily or weekly. Ex. 1008 (Wakeling 1991); Ex. 1009 (Wakeling

1992); Ex. 1028 (Wakeling 1993); Ex. 1018 (Osborne 1995); Ex. 1005 (McLeskey). Dr. Oleksowicz argues that "[i]ntramuscular monthly doses of fulvestrant were repeatedly disclosed in the art." Ex. 1004 at ¶ 138. However, only the Howell and Dukes papers disclose intramuscular monthly dosing.[2]

82. Noting that "[l]arge-animal studies also disclosed i.m. administration," Ex. 1004 at ¶ 140, Dr. Oleksowicz's declaration ignores that large animal studies, *i.e.*, monkeys, also disclosed subcutaneous administration. Ex. 1008 (Wakeling 1991); Ex. 1025 (Dukes 1992).

83. Dr. Oleksowicz argues that "[s]everal small-animal studies used a subcutaneous dose" and that "a POSA would understand that—when scaled up and translated to humans—a large-volume dose would preferably be given intramuscularly." Ex. 1004 at ¶ 142. However, formulations meant to be translated to humans are given by the same route. For example, the fulvestrant

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[2] Dr. Oleksowicz's statement that "O'Regan 1998 disclosed that, '[c]linically, [fulvestrant] must be given by depot intramuscular injection because of low oral potency'" is simply O'Regan quoting other literature rather than making any disclosure of her own research. Indeed, O'Regan used a subcutaneous injection in her studies and provided no evidence in her publication at all of potency. The statement that fulvestrant "must be given by depot intramuscular injection" is not based on any data or comparative studies.

formulation in the AstraZeneca Dukes 1989 patent, cited by Dr. Oleksowicz, was administered to rats (small animals) intramuscularly. Ex. 1007 (Dukes 1989). The further statement that "I.M. administration would be expected to enhance [] long-term release" is in itself without basis -- many i.m. formulations provide rapid release of a drug (*e.g.*, Mylan's EpiPen®). The release of a drug is related to the route of administration and the formulation of the drug.

84. Regarding dosing, Dr. Oleksowicz states that Howell 1996 described the results "as showing that therapeutic levels of fulvestrant 'can be achieved and maintained for 1 month following a single i.m. injection of the long-acting formulation used.'" Ex. 1004 at ¶ 143. This is an incorrect description of Howell 1996. Howell 1996, of which I am a co-author, actually reports that "a direct pharmacokinetic - pharmacodynamic link [was] not proven with the few patients studied to date" and that "future larger trials" were needed. Ex. 1006 (Howell 1996) at 6.

85. Additionally regarding dose, the section of Dr. Oleksowicz's declaration entitled "Dose of Fulvestrant As-Formulated" argues that AstraZeneca selected a 5 ml volume because "injection volumes of 5 ml were known in the art." Ex. 1004 at ¶ 146. But no skilled person would develop a drug based on maximum tolerated injection volume and then determine the dose. Instead, a skilled person would look to deliver a selected dose to achieve therapeutic blood levels and then

decide what volume should be delivered based on the formulation.

86. Dr. Oleksowicz also incorrectly starts with the injection volume to match up the concentration used in McLeskey with the claims. Ex. 1004 at ¶¶ 152-155. McLeskey discloses a 50 mg/ml concentration of fulvestrant which Dr. Oleksowicz scales up backwards to 5 mL to get a 250 mg dose. But, in fact, the proper scaled up calculation of the concentration used in McLeskey shows that the point of the formulations used in that study was to provide the type of maximal bolus doses used in basic biology research, not treatment. An ordinary researcher would recognize that the arachis oil and castor oil formulations were dosed "5 mg in 0.1 ml of vehicle every week" (Ex. 1005 (McLeskey) at 2) to mice, which would roughly translate to a human equivalent dose of approximately 12,000 mg per week using a mg/kg dose approximation (assuming the average weight of a mouse is 0.025 kg and the average weight of a human is 60.0 kg), which would have been equivalent to giving 240 ml per week to a human. A POSA would not look to a formulation such as McLeskey where 300 times the animal dose (which was identified as a "treatment failure") would be administered to humans and expect success. Furthermore, while Dr. Oleksowicz notes that "Howell 1995 and Howell 1996 disclosed i.m. doses of 250 mg" she ignores Howell's conclusion that a lower dose should be explored. Ex. 1004 at ¶ 154; Ex. 1006 (Howell 1996) at 6 ("[L]ower doses of the drug may be effective in

maintaining therapeutic serum drug levels, although further clinical studies are required to confirm this hypothesis.").

XI) REFERENCES CITED IN THE PETITION

87. In Mylan's Petition and accompanying clinician declaration, Mylan and Dr. Oleksowicz select a very specific set of references as showing the scope of prior art at the time of the invention. Petition at 19-28; Ex. 1004 at ¶¶ 50-109. This selection looks backwards from the present day, ignoring the perspective that a skilled clinician would have had at the time of invention. As I discuss above, the universe of options for therapeutic agents available to a clinician was broad, with many options available for each important consideration, like active, administration method and amount (dosing). In my view, the references in the Petition and declaration are not representative of the full scope or content of the prior art, nor of the knowledge or skill of a person of ordinary skill in the art at the time of the invention. I address each of the references cited below.

A) McLeskey (Ex. 1005)

88. McLeskey does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract." Further, McLeskey does not disclose "administering intramuscularly to a human in need of such treatment." Additionally, McLeskey does not disclose the limitations: "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5

$ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (*i.e.*, individual).

89. McLeskey is a basic science research paper designed to investigate an artificial hormone independent mouse tumor model related to growth factor signaling pathways.

90. McLeskey states that model systems using FGF-transfected MCF-7 cells "have been described previously." Ex. 1005 at 2. McLeskey explains that these cell lines "allow[] effects of FGF overexpression on metastatic capability to be assessed by X-gal staining of organs and tissues of tumor-bearing mice." Ex. 1005 at 2. Based on the use in McLeskey of FGF-transfected MCF-7 cells, the skilled artisan would know that McLeskey continues a line of research into hormone independent pathways of tamoxifen resistance. The authors injected the cells into mice and used this model to evaluate whether tamoxifen resistance is related to FGF signaling pathways.

91. McLeskey lists two formulations of fulvestrant. First, "powdered drug was [] dissolved in 100% ethanol and spiked into warmed peanut oil." Ex. 1005 at 2. Second, "50 mg/ml preformulated drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil was supplied by B.M. Vose (Zeneca Pharmaceuticals)." Ex. 1005 at 2. These formulations were

treated as interchangeable for the purposes of the research study. Dr. Oleksowicz does not dispute that McLeskey did not disclose the units in the castor oil formulation.

92. The studies in McLeskey were not designed to evaluate the treatment of any disease with fulvestrant; instead, four different actives, tamoxifen, 4-OHA, letrozole, and ICI 182,780 (fulvestrant) were used as a research tool to assess a model of FGF-mediated tumor growth. The animal formulations administered in McLeskey included sustained-release tamoxifen pellets, letrozole in a liquid vehicle of 0.3% hydroxypropyl cellulose via gavage, 4-OHA (formestane) in an aqueous vehicle of 0.3% hydroxypropyl cellulose by subcutaneous injection, and two fulvestrant formulations—50 mg/ml preformulated drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil, and powdered drug dissolved in 100% ethanol and spiked into warmed peanut oil to give a final concentration of 50 mg/ml—by subcutaneous injection.

93. McLeskey provides no data related to safe or effective treatment of humans or animals -- indeed, McLeskey indicates that none of the test drugs slowed tumor growth. Ex. 1005 at 1. McLeskey calls the inability of fulvestrant to affect the estrogen-independent *in vivo* growth of FGF-transfected MCF-7 cells a "treatment failure." Ex. 1005 at 10. "[T]he insensitivity of the estrogen-independent *in vivo* growth of the FGF transfectants to [fulvestrant] or the

aromatase inhibitors implies that clinical tamoxifen resistance due to FGF receptor-mediated signaling may not respond to a second hormonal therapy." Ex. 1005 at 11 (emphasis added). Because fulvestrant was ineffective, McLeskey proposes that "[t]herapy . . . with agents directed against the autocrine or paracrine effects of FGFs might result in beneficial effects." Ex. 1005 at 12-13.

94. McLeskey provides no blood plasma fulvestrant concentration levels in mice after subcutaneous administration of any of the experimental drug formulations used—not for fulvestrant or the aromatase inhibitors or tamoxifen, nor did McLeskey administer an "intramuscular injection" to "a human in need." For the experiment in mice, fulvestrant was administered "5 mg s.c. [subcutaneous] every week." Ex. 1005 at 5. Thus, from a clinician's perspective, it does not teach treatment of humans or minimum plasma levels.

95. McLeskey also provides no solubility or other data for any of the formulations used.

B) Howell 1995 (Ex. 1012)

96. I am an author of Howell 1995. Howell 1995 does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Further, Howell 1995 does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the

therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$."

97. Howell 1995 says that fulvestrant is "a steroidal antioestrogen" and mentions evidence that fulvestrant "prevents dimerisation of two molecules of the oestrogen receptor which is a prerequisite for gene transcription." Ex. 1012 at 1. Howell 1995 reports preliminary results from treating 19 postmenopausal patients with "monthly intramuscular injections of ICI 182780 after progression on tamoxifen, for a median duration of 18 months." Ex. 1012 at 1. "ICI 182780 was administered as a long-acting formulation in a castor oil-based vehicle by monthly intramuscular injection." Ex. 1012 at 1. Howell 1995 provides no additional information on the formulation used and provides no blood plasma fulvestrant concentration levels.

98. Nineteen patients were treated with 7 showing partial responses. This is clearly an early stage research trial as described above, given its limited number of patients with advanced disease who were highly selected and the lack of a control group of patients (*e.g.*, treated with the standard endocrine agent at that time).

99. A person of ordinary skill in the art would interpret the results reported in Howell 1995 with caution, because the study used only 19 patients, administered a first dose of 100 mg to the first four patients as a "safety appraisal," did not have

a control group, and was not blinded. Ex. 1012 at 1.

C) Howell 1996 (Ex. 1006)

100. I am an author of Howell 1996 which relates to the same 19 patients as Howell 1995. Howell 1996 does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Howell 1996 administered a dose of 250 mg but concluded that "lower doses of the drug may be effective in maintaining therapeutic serum drug levels" so an ordinary researcher would have been motivated to use lower doses. Ex. 1006 (Howell 1996) at 6. Howell 1996 does not disclose the composition of the administered formulation of fulvestrant and the skilled artisan would not be able to use the data in Howell 1996 to obtain the claimed method of treatment invention.

101. Howell 1996 is a more extensive report of the same study reported in Howell 1995 that administered a monthly depot intramuscular injection of fulvestrant "contained in a castor oil-based vehicle" to 19 patients. Ex. 1006 at 2. Serum levels of fulvestrant were measured in 15 patients that were started on 250 mg in the first month and 11 patients in the sixth month. Ex. 1006 at 3. Even at month 6, the mean end-of-month plasma concentration of 5.6 ng ml^{-1} was below 8.5 $ngml^{-1}$. Based on this data, a skilled artisan would have known that 250 mg monthly fulvestrant would not achieve 8.5 $ngml^{-1}$ "for at least four weeks" in this

population in the method described by Howell 1996. Dr. Oleksowicz does not address the requirement for the blood level to be maintained "for at least four weeks" when she refers to the "mean C_{max} of 10.5 $ngml^{-1}$ in patients first-dosed with 250 mg fulvestrant, and a mean C_{max} of 12.8 $ngml^{-1}$ in patients having received six once-monthly 250 mg doses of fulvestrant." Ex. 1004 at ¶ 58. The mean C_{max} is not the average blood level over the four week period but rather the C_{max} is the average peak concentration during the four week period. Howell 1996 states that in his study C_{max} occurred around days 8 and 9. Ex. 1006 at 3 ("In the majority of patients, the measured C_{max} was reached 8 or 9 days after the start of the drug administration."). As can be seen from Figure 2 in Howell 1996, the blood level of fulvestrant then dropped off over the rest of the four week period until it reached its trough level on day 28—which was always below 8.5 $ngml^{-1}$. Ex. 1006 at 4. Therefore, it is clear from the method in Howell 1996 that 250 mg monthly fulvestrant would not achieve 8.5 $ngml^{-1}$ "for at least four weeks."

102. Importantly, Howell 1996 also states that "[t]here was no significant difference in the median C_{max} and AUC between responders and non-responders to treatment." Ex. 1006 at 3. Additionally, "[a]fter 6 months of treatment there was no significant difference between C_{max} and AUC for patients who had a partial response (PR) compared with those with a no change (NC) response." Ex. 1006 at 3. Accordingly, Howell 1996 concluded that "a direct pharmacokinetic -

pharmacodynamic link is not proven with the few patients studied to date." Ex. 1006 at 6. This means that not only were no therapeutic blood levels determined, but also that no correlation between blood levels and clinical activity was found.

103. Howell 1996 encouraged a skilled artisan to seek lower blood levels of fulvestrant than achieved in Howell 1996. Ex. 1006 at 6. Howell 1996 said that "lower doses of the drug may be effective in maintaining therapeutic serum drug levels, although further clinical studies are required to confirm this hypothesis." Ex. 1006 at 6; *see also* Ex. 1006 at 7 ("At the dose used, there was accumulation of the drug over time and thus lower doses than those administered in this study may be as effective."). Indeed, AstraZeneca in its subsequent clinical studies did precisely that including a 125 mg dose. Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002). These statements in Howell 1996 would suggest to the skilled artisan that increasing the blood plasma concentration would not result in greater clinical benefit.

104. Dr. Oleksowicz's statement that "Howell 1996 specifically predicted that blood plasma fulvestrant concentration levels of 2-3 ng/ml 'were consistent with a therapeutic effect in patients with advanced breast cancer'" is misleading. Ex. 1004 at ¶ 60. In context, Howell explains that the original dose was selected based on "predicted" levels of 2-3 ng/ml from monkey and biological marker studies. Ex. 1006 at 6. But, the Howell 1996 study concluded that based on the

clinical data "a direct pharmacokinetic-pharmacodynamic link is not proven with the few patients studied to date." *Id.* (emphasis added). After the Howell data, the researchers determined this dose may be too high and suggested further research to decrease the dose. *Id.* ("These data suggest that lower doses of the drug may be effective in maintaining therapeutic serum drug levels, although further clinical studies are required to confirm the hypothesis.").

105. Dr. Oleksowicz further argues that "[i]t would be a routine and predictable method of optimization for a POSA to measure a patient's blood plasma fulvestrant concentration and to adjust the amount and frequency of fulvestrant administered to achieve concentrations at or above 8.5 $ngml^{-1}$ for 4 weeks." Ex. 1004 at ¶ 229. I am not a formulator so I will not be opining on this issue; instead I defer to Dr. Illum, a formulation expert, who I understand has concurrently submitted a declaration in support of AstraZeneca's preliminary response. Being that Dr. Oleksowicz is also not a formulator, I do not see how she is competent to opine on this issue. However, from a clinician's perspective, there would be no reason for a POSA to "adjust the amount and frequency of fulvestrant administered to achieve concentrations at or above 8.5 $ngml^{-1}$ for 4 weeks" because Howell 1996 suggested a lower dose. Dr. Oleksowicz's idea that it would be routine and predictable to optimize giving a formulation for a longer duration does not explain why a POSA would want to do so. It does not matter that a POSA

could do it—there is no reason why a POSA would want to do it here especially in light of Howell 1996 which suggested the opposite.

106. A person of ordinary skill in the art would have interpreted the results reported in Howell 1995 and 1996 with caution, because the study used only 19 patients, administered a first dose of 100 mg to the first four patients for "appraisal of drug safety," did not have a control group, and was not blinded. Ex. 1006 at 2. Howell 1996 further explained that tamoxifen was known to stimulate tumor growth and that the withdrawal of tamoxifen from patients in this study could account for some of the responses seen in the study. Ex. 1006 at 7. Finally, Howell 1996 noted that the results needed to be confirmed in "future larger trials." Ex. 1006 at 6. As noted above, Dr. Howell reiterated his note of caution when he wrote that "phase II studies are notoriously unreliable in predicting superiority over old agents." Ex. 2040 (Howell 1997) at 3-4. This trial, as noted above in the description of Howell 1995 (the same study), is an early stage research trial with a limited number of patients with advanced disease and lack of controls. The skilled artisan would know that drug candidates with encouraging phase II clinical results more often than not fail to reach market, especially in the area of treatment for breast cancer.

D) Dukes 1989 (Ex. 1007)

107. Dukes 1989 does not disclose a "method for treating a hormonal

dependent benign or malignant disease of the breast or reproductive tract" or "administering . . . to a human in need of such treatment." Dukes 1989 does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Further, Dukes 1989 does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$."

108. Dukes 1989 relates to therapeutic products comprising an estrogen and a pure antiestrogen for use in treating perimenopausal and postmenopausal conditions. Examples 1-3 of Dukes 1989 describe experimental formulations given to rats. Example 1 provides an oily solution in arachis oil, administered subcutaneously. Ex. 1007 at 7. Example 2 provides a daily intramuscular injection of an aqueous solution, comprising 25 mg fulvestrant, 100 mg ethanol (96%), 100 mg water, 20 mg poloxamer 407 and sufficient propylene glycol to bring the solution to a volume of 1 ml. *Id.* at 8. Example 3 provides a formulation of "50 mg of [fulvestrant], 400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml." *Id.* at 9. A person of ordinary skill in the art would understand this latter formulation to have 50 mg/ml of fulvestrant, 40% w/v of benzyl alcohol and sufficient castor oil to bring to volume. This

formulation was administered by intramuscular injection to rats every two weeks.

109. Dukes 1989 does not provide any information regarding fulvestrant blood levels in the experimental animals; thus, it provides no guidance for a clinician. From a clinician's perspective, Dukes 1989 does not teach intramuscular injection of fulvestrant with the combination of formulation excipients in their respective amounts, or minimum plasma levels.

E) Wakeling 1991 (Ex. 1008)

110. Wakeling 1991 does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract" or "administering intramuscularly to a human in need of such treatment." Wakeling 1991 does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Further, Wakeling 1991 does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (*i.e.*, individual).

111. Wakeling 1991 reports on the antiestrogen effects of fulvestrant in rats and monkeys after subcutaneous injection of a peanut oil suspension. The paper also refers to another pure antiestrogen, ICI 164,384. Wakeling 1991 teaches only research formulations for use in animals, prepared immediately before use. Stock

solutions of tamoxifen, a metabolite of tamoxifen (ICI 164,384), and fulvestrant (ICI 182,780) were "prepared in ethanol, stored at 4˚C, and diluted as required." Ex. 1008 at 1. Immediately before use, fulvestrant was "prepared for administration by diluting an ethanol stock solution into the required volume of arachis oil with gentle warming." *Id.* at 2. This "oil suspension" formulation was administered by subcutaneous injection to rats. *Id.* at 3.

112. Dr. Oleksowicz mistakenly states that Wakeling 1991 disclosed subcutaneous administration "once-per-4-week" in nude mice. Ex. 1004 at ¶ 65. What Wakeling 1991 actually discloses is that the nude mice were administered "***a single parenteral dose*** of ICI 182,780 in oil suspension" and notes that biological effects of this subcutaneous "bolus"[3] dose lasted for four weeks. Ex. 1008 at 1 (emphasis added). That does not mean that the formulation was dosed once every four weeks, and also does not mean that plasma levels were sustained for four weeks. Indeed, there is no discussion of plasma levels in Wakeling 1991. This same experiment (with the same limitations) is also discussed in Wakeling 1992 and 1993.

113. Notably, Wakeling 1991 also investigates the estrogenic/anti-estrogenic effects of an oral administration of fulvestrant in rats, and finds some anti-uterotropic activity qualitatively similar to the fulvestrant given

[3] A bolus dose is a *single* large dose given all at once.

subcutaneously, but with a reduced potency. Ex. 1008 at 2-3 ("The effects of ICI 182,780 administered p.o. were qualitatively similar but potency was reduced by an order of magnitude compared with s.c. dosing[.]"). Thus, Wakeling 1991 disclosed that oral administration of fulvestrant was a viable (though challenging) option, and would encourage further formulation work on oral administration, given the incentives to do so described above.

114. Wakeling 1991 does not provide any information regarding fulvestrant blood levels in the experimental animals; thus, it provides no guidance for a clinician. From a clinician's perspective, this reference does not teach treatment of humans, intramuscular injection of fulvestrant with the combination of formulation excipients in their respective amounts, dosing frequency, or minimum plasma levels.

F) Wakeling 1992 (Ex. 1009)

115. Wakeling 1992 does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract" or "administering intramuscularly to a human in need of such treatment." Wakeling 1992 does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Further, Wakeling 1992 does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at

least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (*i.e.*, individual).

116. Wakeling 1992, like Wakeling 1991, investigates the biochemical activity of the fulvestrant compound in rats. The authors investigate the activity of various anti-estrogenic compounds in tissue culture, rats, pigtail monkeys, and xenografts of two types of cancer cells in mice. Wakeling 1992 is a basic research paper.

117. Similar to Wakeling 1991, Wakeling 1992 uses a peanut oil suspension administered subcutaneously to mice and finds that a "bolus" dose of ICI 182,780 in arachis oil, administered subcutaneously, achieved anti-oestrogenic activity for in excess of 1 month in both rats and monkeys. Ex. 1009 at 1. Again, Wakeling 1992 provides no information regarding fulvestrant blood levels, much less any guidance for a clinician regarding therapeutically effective blood levels of fulvestrant for treating breast cancer in humans. Wakeling 1992 also refers to another pure antiestrogen, ICI 164,384. Wakeling 1992 treats fulvestrant as a research tool, saying it "provides the opportunity to evaluate clinically the potential therapeutic benefits of complete blockade of oestrogen effects in endocrine-responsive human breast cancer" and "will be used to test" whether or not the category of pure antiestrogens have a place in breast cancer treatment, showing that the category of pure antiestrogens' role in human cancer treatment was

uncertain, including fulvestrant. Ex. 1009 at 1, 4.

118. As in Wakeling 1991, the formulations described in Wakeling 1992 are experimental formulations for research in animals. There is no information regarding fulvestrant blood levels in the experimental animals; thus, it provides no guidance for a clinician. From a clinician's perspective, this reference does not teach treatment of humans, intramuscular injection of fulvestrant with the combination of formulation excipients in their respective amounts, dosing frequency, or minimum plasma levels.

G) Dukes 1992 (Ex. 1025)

119. Dukes 1992 does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract" or "administering . . . to a human in need of such treatment." Dukes 1992 does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Further, Dukes 1992 does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (*i.e.*, individual).

120. Dukes 1992 is concerned with an animal study that investigated the effects of fulvestrant on the uterus of overiectomized, oestrogen-treated monkeys.

In essence, this is a study of an MRI imaging protocol in monkeys, where the goal is to deliver fulvestrant to the experimental animal to evaluate its effects *in vivo*.

121. Dukes 1992 explains that the propylene glycol and castor oil based formulations were experimental formulations, meant to "facilitate other investigations of [fulvestrant]." Ex. 1025 at 6. No other components of the formulation were disclosed. In addition to those experimental formulations, Dukes 1992 discusses two other fulvestrant formulations for subcutaneous administration: an arachis oil suspension; and a propylene glycol solution.

122. Dukes 1992 notes that "these studies revealed a differential response to oestradiol between the myometrium and endometrium, where the endometrium appeared more sensitive, as reflected by a more rapid recovery from antioestrogen blockade." Ex. 1025 at 9. Based on the variability of fulvestrant's effects on two different tissues in the same *organ*, in the same species, a clinician would be reluctant to predict the effects of fulvestrant in *other* tissues, which might also be different from the tissues studied in unpredictable ways.

123. Dr. Oleksowicz argues that because "[t]he treatment completely blocked uterotrophic action of estradiol for 3-4 weeks" Dukes 1992 characterized this as "confirm[ing] fulvestrant's 'sustained antiuterotrophic action.'" Ex. 1004 at ¶ 73. I do not see how this is relevant to the claimed method of treatment which claims ***blood plasma fulvestrant concentrations*** that are achieved and maintained

for a month, not antiuterotrophic activity that is observed for a month. "Sustained [] action" for 3-4 weeks does not equate to blood plasma levels.

124. Dr. Oleksowicz also states that the results reported in Dukes 1992 "'confirmed' that 'the duration of action of a single i.m. injection of [fulvestrant] was dose-related." Ex. 1004 at ¶ 74. But, again, the duration of biological effect being related to an initial dose is not equivalent to therapeutic blood plasma levels, which is what is required by the claims.

125. From a clinician's perspective, Dukes 1992 does not teach treatment of humans, intramuscular injection of fulvestrant with the combination of formulation excipients in their respective amounts, or minimum plasma levels.

H) Wakeling 1993 (Ex. 1028)

126. Wakeling 1993 does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract" or "administering intramuscularly to a human in need of such treatment." Wakeling 1993 does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Further, Wakeling 1993 does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (*i.e.*, individual).

127. This review article discusses both fulvestrant and ICI 164,384, and summarizes the ongoing research into the safety and effectiveness of pure antiestrogens for cancer treatment. Dr. Oleksowicz states that "[f]ulvestrant, a pure antiestrogen, was recognized as potentially being important in the 'therapeutic application in the treatment of breast cancer,'" suggesting that it was a conclusion of the Wakeling 1993 researchers that fulvestrant would be effective. Ex. 1004 at ¶ 79. In reality, Wakeling 1993 indicated that fulvestrant did have "potential" but that further research was needed to determine its usefulness as a treatment for breast cancer. It further notes the risk of using a pure antiestrogen as a breast cancer treatment: "[o]ne predicted undesirable action of pure antiestrogens in therapeutic use may be a tendency to reduce bone density and hence to precipitate or exacerbate osteoporosis." Ex. 1028 at 7.

128. All three Wakeling publications (1991, 1992, and 1993) are early work evaluating the action of the fulvestrant compound in animal models, and not papers about the development of formulations for fulvestrant.

129. Wakeling 1993 discloses only early stage animal research subcutaneous formulations of fulvestrant in arachis oil. From a clinician's perspective, it does not teach treatment of humans, intramuscular injection of fulvestrant with the combination of formulation excipients in their respective amounts, dosing frequency, or minimum plasma levels.

I) Dukes 1993 (Ex. 1026)

130. Dukes 1993 does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract" or "administering . . . to a human in need of such treatment." Dukes 1993 does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Further, Dukes 1993 does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (*i.e.*, individual).

131. While Dukes 1992 studied the effect of fulvestrant on ovariectomised monkeys, Dukes 1993 studied the effect of fulvestrant on intact monkeys with normal menstrual cycles. Just as in Dukes 1992, this is a study of an MRI imaging protocol in monkeys, where the goal is to deliver fulvestrant to the experimental animal to evaluate its effects *in vivo*, and not to formulate it for safety, tolerability, or effectiveness in humans.

132. Dukes 1993 reports the use of two fulvestrant formulations for intramuscular administration: a short-acting propylene glycol formulation, administered once daily for 25 days; and a long-acting castor oil formulation given as a single intramuscular injection. Ex. 1026 at 2. No excipients or other

components are identified, and there is no information regarding fulvestrant blood levels in the experimental animals; thus, it provides no guidance for a clinician.

133. Dukes 1993 reports that "[w]hen the occurrence of ovulation was accounted for, no significant differences emerged between the effects of the different formulations and doses of [fulvestrant], with the exception that the 2.5 mg dose (F2) appeared slightly less effective ($P<0.05$) than the 4.0 mg dose in the second half of the cycle." *Id.* at 5. Dukes 1993 notes that "the mean response concealed wide differences between individual monkeys with five of the seven animals showing shrinkage (mean - 35 ± 5%), whilst the remaining two monkeys experienced net growth of the endometrium (+ 103% and + 28%)." *Id.* at 6. Dukes 1993 reports, under "Results": "Tissue volumes varied widely between individuals but less so in repeat measurements in the same animal." *Id.* at 2. This shows that in normal (non-ovariectomised) animals the variability in these measurements is large, and hence it is difficult to prove significant differences between treatments unless a large number of animals are used. Further, "[t]he reasons for the variability between individuals in their susceptibility to blockade of ovulation are not understood." *Id.* at 7. Dukes 1993 also reports that "the threshold of sensitivity of the myometrium to oestrogens is higher than that of the endometrium," further highlighting the variability within two different tissues in the same organ, in the same species. *Id.* at 7. Dukes 1993 concludes that "[t]he

clinical usefulness of [fulvestrant] remains to be determined." *Id.* at 7.

134. Dukes 1993 discloses only early stage animal research intramuscular formulations of fulvestrant in castor oil and propylene glycol. From a clinician's perspective, it does not teach treatment of humans, intramuscular injection of fulvestrant with the combination of formulation excipients in their respective amounts, or minimum plasma levels.

J) DeFriend 1994 (Ex. 1027)

135. DeFriend 1994 does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Further, DeFriend 1994 does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$."

136. DeFriend 1994 is not a treatment study. It is a first-in-humans study to evaluate the biological activity of fulvestrant as an estrogen antagonist in primary breast tumors *in vivo*. DeFriend 1994 studied pharmacodynamic indicators of antiestrogen activity in fifty-six patients with primary breast cancer that were administered fulvestrant prior to receiving primary breast surgery. Ex. 1027 at 1. The study in DeFriend 1994 administered 7 daily doses of 6 mg or 18 mg i.m. injection of "a short-acting formulation, containing 20 mg/ml drug in a propylene

glycol-based vehicle." Ex. 1027 at 2.

137. DeFriend 1994 reports that "[a]nimal studies have demonstrated considerable interspecies variability in the elimination half-life of [fulvestrant], with a half-life of about 4 h in rats and 2 days in dogs after i.m. administration." Ex. 1027 at 5. In other words, that the translation of pharmacokinetic information from one species to another would be very different. DeFriend 1994 concluded that "[t]his small study has shown [fulvestrant] to be well tolerated after short term administration and has produced preliminary evidence to suggest that this novel agent does exhibit biological activity as an estrogen antagonist in primary breast tumors, without producing demonstrable agonist effects." Ex. 1027 at 6. The study does not investigate whether fulvestrant is an effective treatment for breast cancer, and the authors conclude only that fulvestrant should be further evaluated to determine "whether a pure estrogen receptor antagonist offers any additional benefits in the treatment of human breast cancer" over traditional treatments such as tamoxifen. Ex. 1027 at 1. In particular, the authors caution that "the pure [estrogen] antagonist profile of activity of ICI 182780 in human subjects will need to be confirmed in future clinical studies." Ex. 1027 at 5. In other words, DeFriend 1994 concludes, that while fulvestrant had potential, its efficacy on disease was unknown.

138. DeFriend 1994 provides some pharmacokinetic data in Figure 1,

however that figure does not teach therapeutically significant fulvestrant blood plasma concentrations over 4 weeks from one dose. Figure 1 merely shows that there is some accumulation of fulvestrant in the blood stream after repeated injections. Dr. Oleksowicz notes that "[t]he study found that blood serum fulvestrant concentration was 'dose dependent.'" Ex. 1004 at ¶ 91. However, Dr. Oleksowicz fails to recognize that DeFriend 1994 did not show a dose effect on estrogen and progesterone expression, as there was no significant difference between the 6 and the 18 mg doses, *i.e.*, there was no correlation between the level of fulvestrant in the blood and the activity seen in the tumors. In any case, Dr. Oleksowicz's citation to serum concentration as "dose dependent" relates to the propylene glycol-based formulation used in DeFriend 1994. The paper does not teach the ordinary researcher anything about any other formulation.

139. The planned study using a long-acting castor oil based fulvestrant formulation, mentioned in DeFriend 1994 (Ex. 1027 at 5), was intended to seek early evidence of inhibitory activity of the compound on human breast cancer and to address the question of whether the adverse effects seen in the present studies were due to the drug itself or to the propylene glycol based formulation, as noted in the reference itself: "It is possible, therefore, that these adverse events were related either to the drug itself or to the propylene glycol-based vehicle used in the short-acting formulation. This question will be addressed in future studies which are

planned with a different, long-acting, formulation of ICI 182780 contained in a castor-oil based vehicle." *Id.* at 5. DeFriend 1994 does not provide any further information regarding the components of this long-acting castor oil based fulvestrant formulation.

K) Osborne 1995 (Ex. 1018)

140. Osborne 1995 does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract" or "administering intramuscularly to a human in need of such treatment." Osborne 1995 does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Further, Osborne 1995 does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (*i.e.*, individual).

141. The Osborne 1995 publication is a report of basic science research, where the authors implanted human estrogen receptor positive breast cancer cells (MCF-7) into athymic nude mice (*i.e.*, mice that would not reject the tumor cells). The authors report on fulvestrant's effects against tamoxifen-resistant cancer growth in this experimental, modified animal model.

142. Osborne 1995 reports that a castor oil formulation of ICI 182,780,

administered subcutaneously once weekly, suppressed tumor growth and tumorigenesis in this experimental model. No further details are provided regarding the castor oil formulation. Dr. Osborne noted that "[e]ven if pure antiestrogens are shown to have superior antitumor activity in women with breast cancer, they may not be the optimal antiestrogen for clinical use." Ex. 1018 at 5. Dr. Osborne highlighted potential risks of treatment with fulvestrant, including that "[o]n the basis of our data, we would predict that most patients with ICI 182,780-resistant tumors, would not respond well to subsequent treatment with tamoxifen." *Id.* Indeed, as previously noted, Dr. Osborne's concern in 1995 appeared to be supported through the first clinical study (Howell 1995/1996) where the issue of hormone insensitivity following fulvestrant resistance was raised and discussed in Robertson 1997. Ex. 2041 (Robertson 1997) at 3. Furthermore, Dr. Osborne noted that "[t]he estrogenic properties of tamoxifen in bone and on blood lipids may help to reduce bone loss and prevent cardiovascular disease." Ex. 1018 at 5. But, Dr. Osborne continued that "[t]he effect of ICI 182,780 on these parameters is not yet known, but it might be deleterious given its lack of estrogenic qualities." *Id.*

143. Osborne 1995 is related to the use of a particular modified mouse model for experimental investigation of tamoxifen-resistant cancer growth, and not related to development of fulvestrant formulations. The formulations described are experimental formulations for research in an animal model, and there is no

information regarding fulvestrant blood levels. It provides no guidance for a clinician seeking to treat patients for human breast cancer.

L) O'Regan 1998 (Ex. 1013)

144. O'Regan 1998 does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract" or "administering intramuscularly to a human in need of such treatment." O'Regan 1998 does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Further, O'Regan 1998 does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (*i.e.*, individual).

145. O'Regan 1998 describes a study in ovariectomized mice with implanted endometrial tumors, evaluating the risks of promoting endometrial cancer after treatment with toremifene or fulvestrant. The only fulvestrant formulation used in O'Regan 1998 was dissolved in ethanol and administered in peanut oil (following the evaporation of the ethanol under N_2) to mice by subcutaneous injection.

146. To the extent it cites to Howell 1996, O'Regan 1998 makes the point that it is an early stage study -- "there are not the same stringent requirements for a

drug that is used as a palliative therapy in advanced disease compared with drugs that are used for long-term adjuvant therapy." Ex. 1013 at 2. And, O'Regan 1998 observes that "[c]learly, a woman should not be led to believe that no risks exist because inadequate and early clinical studies are being reported." *Id.* at 5.

XII) THE CLAIMS OF THE '680 PATENT ARE NOT OBVIOUS

A) Ground One: McLeskey

1) McLeskey Alone Fails To Disclose Nearly All Of The Limitations Of The '680 Patent Claims

147. Dr. Oleksowicz argues that "claims 1-20 of the '680 patent were obvious to a POSA in view of McLeskey, which ***disclosed the precise formulation of fulvestrant claimed*** in the patent," "[a] POSA seeking therapeutic formulations of fulvestrant would find McLeskey, which ***disclosed every element of the claimed formulation***," and "McLeskey ***disclosed the exact concentrations of excipients*** claimed in independent claims 1and 9: 10% ***w/v*** of ethanol, 10% ***w/v*** of benzyl alcohol, 15% ***w/v*** of benzyl benzoate, and a sufficient amount of a castor oil vehicle." Ex. 1004 at ¶¶ 162-164 (emphases added). First, McLeskey does not disclose "the *exact* concentrations of excipients." It is clear to a skilled person that there are no units disclosed in McLeskey, therefore these cannot be the *exact* concentrations disclosed in the claims. Second, Dr. Oleksowicz tellingly analyzes only the ingredients of the claims against McLeskey. Ex. 1004 at Table 2. The claims are to a method of treatment. As shown in the table that follows and

discussed in more detail below, every other element of the claimed method of treatment is missing from McLeskey.[4]

'680 Patent Claim Limitations	McLeskey
A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising	NOT hormonal dependent . . . "hormone independent" NOT treatment . . . "treatment failure" NOT malignant disease of the breast . . . genetically engineered model
administering intramuscularly	NOT intramuscular . . . "subcutaneous"
to a human in need of such treatment a formulation comprising	NOT human . . . mice
wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at	NO blood plasma levels NOT therapeutically significant . . . "treatment failure"

[4] Dr. Oleksowicz's attempt to separate the formulation from both the route and schedule of administration is improper. As discussed above, one cannot simply take a formulation using one route of administration and schedule and expect to achieve the same results when using it with another route of administration and schedule.

least 2.5 ngml^{-1} [8.5 ngml^{-1}] for at least four weeks.	NOT once every four weeks . . . "once weekly"

148. These missing limitations from McLeskey were acknowledged by the Examiner during the prosecution of the '680 Patent. Ex. 1002 at 313 ("Mc[L]eskey et al. teaches a studies employing subcutaneous injection of fulvestrant to nude mice. . . . Mc[L]eskey et al. does not expressly teach the use of fulvestrant in treating hormonal dependent diseases of the breast. It does not expressly teach the dosing regimen to be once a month, intramuscular administration, or the volume administered. Mc[L]eskey et al. does not expressly teach the herein claimed serum concentration of fulvestrant.").

2) A Skilled Artisan Would Not Look to McLeskey

149. A skilled artisan looking for a treatment for hormonal dependent disease[5] would not look to McLeskey. The skilled artisan, and, in particular, such a person engaged in the clinical treatment of hormonal dependent diseases of the breast and/or reproductive tract and hoping to develop a treatment for such diseases, would not have considered McLeskey relevant. The title of McLeskey

[5] All of the patent claims of the '680 Patent are directed to a "method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract." Ex. 1001 ('680 Patent).

teaches that fulvestrant was unsuccessful in the McLeskey model: "Tamoxifen-resistant Fibroblast Growth Factor-transfected MCF-7 Cells Are Cross-Resistant *in Vivo* to the Antiestrogen ICI 182,780 [fulvestrant] and Two Aromatase Inhibitors." Ex. 1005 at 1. McLeskey repeatedly indicates that the mouse model being studied is "hormonal independent." Ex. 1005 at 12 ("[T]hese data provide evidence for a mechanism by which FGF-stimulated estrogen-independent growth bypasses the ER signal transduction pathway . . . . [O]ur studies implicate direct action by FGFs in the estrogen-independent growth produced by transfection of either FGF-4 or FGF-1 into MCF-7 cells."). Even if the skilled artisan had read the full publication, McLeskey would have encouraged the skilled artisan to study growth factor inhibitors to solve tamoxifen resistance—not endocrine therapies, such as fulvestrant, which failed to inhibit tumor growth or metastases in the animal model studied.

150. To begin, I disagree that "[t]he POSA would have immediately found McLeskey" or that "[t]he POSA could have [] easily come across McLeskey." Petition at 51. According to the publisher, the full text of the issue of the journal in which McLeskey appeared was not searchable online prior to the invention of the '680 Patent. Ex. 2042 (AACR Journals Online); Ex. 2125 (Affidavit of Internet Archive).

151. Dr. Oleksowicz argues that "McLeskey disclosed the use of

fulvestrant as a possible alternative for tamoxifen in the treatment of ER+ breast cancer, and recognized the need for new clinical treatments for human patients." Ex. 1004 at ¶ 166. But McLeskey is not about using fulvestrant as an alternative treatment for ER+ hormone dependent breast cancer—it identifies the limitations of endocrine therapy due to alternate mechanisms of resistance, identifies growth-factor mediated alternatives for treatment, and recommends treatments based on targeting these growth factors. Ex. 1005 at 1. McLeskey says nothing about the use of fulvestrant for the treatment of breast cancer and, instead, encourages "[t]herapy of such tumors with agents directed against the autocrine or paracrine effects of FGFs might result in beneficial effects." Ex. 1005 at 12-13.

3) McLeskey Is A Study Of Basic Biology Unrelated to Treatment

152. McLeskey is a basic science research paper designed to investigate an artificial hormone independent mouse tumor model related to growth factor signaling pathways. Dr. McLeskey herself stated that the research "was not designed to look at the treatment of any disease with fulvestrant." Ex. 2043 (McLeskey Declaration) at 2. The text of the paper makes that clear.

153. It is undisputed that Dr. McLeskey herself stated that "[t]he paper is clear that the formulations of these drugs were for research purposes for subcutaneous administration to mice--not treatment of humans." Ex. 2043 (McLeskey Declaration) at 2. Indeed, one of ordinary skill would recognize the

formulations used for the McLeskey research to be those for use in animal research, not for human therapy. Dr. Oleksowicz agrees that because of the constraints of animal biology and animal research, for basic biology research like this, special animal research formulations are used. Ex. 1004 at ¶ 169. A skilled researcher would understand that the formulations used for endocrine therapy in McLeskey are all specific for the constraints of working in a mouse model. For example, the tamoxifen pellets used in McLeskey were purchased from Innovative Research of America, a company that specializes in only animal formulations. Ex. 2044 (Innovative Research) at 9 ("All products in this catalog are sold for investigational use in laboratory animals only and are not intended for diagnostic or drug use."). In contrast, for humans, tamoxifen was administered orally in 20 mg tablets. Ex. 2045 (PDR 1999 Nolvadex®) at 4. Similarly, letrozole was administered in McLeskey in a liquid vehicle of 0.3% hydroxypropyl cellulose via gavage—for humans, letrozole was approved and sold as oral tablets, with excipients including ferric oxide, microcrystalline cellulose, and magnesium stearate. Ex. 2046 (PDR 1999 Femara®) at 12. The McLeskey authors administered 4-OHA, also known as formestane, in an aqueous vehicle of 0.3% hydroxypropyl cellulose by subcutaneous injection once daily, six days a week—for humans, a different formulation was approved in Europe for intramuscular injection every two weeks. Ex. 2047 (Santen) at 8.

154. A POSA would have no reason to select the animal research castor oil formulation of McLeskey.

155. Given the difference in formulation and mode and schedule of administration of the other three endocrine agents used in McLeskey (tamoxifen, letrozole, 4-OHA) between this animal research experiment and human treatment, a POSA would not expect that s/he could simply transfer the fulvestrant formulations used in mice and deliver them by a different route and schedule of administration to humans and achieve successful results. This is especially true given that the mode and schedule of administration and formulations for fulvestrant used by McLeskey were a "treatment failure." Not surprisingly, Dr. Oleksowicz provides no explanation for how a POSA would know that using the formulations and route and schedule of administration for fulvestrant in mice would successfully translate to humans.

156. The dosing in McLeskey confirms that the point of the formulations used in the study was to provide the type of maximal doses used in basic biology research, not treatment. An ordinary researcher would recognize that the arachis oil and castor oil fulvestrant formulations were dosed "5 mg in 0.1 ml of vehicle every week" (Ex. 1005 at 2), which would roughly translate to a human equivalent dose of approximately 12,000 mg per week using a mg/kg dose approximation (assuming the average weight of a mouse is 0.025 kg and the

average weight of a human is 60.0 kg), which would have been equivalent to giving 240 ml per week to a human.[6]

157. Dr. Oleksowicz argues that "I.M. injections enable prolonged release of the drug and thereby reduce the number of required injections, which is preferable for patients and physicians/clinicians." Ex. 1004 at ¶ 170. That is not always true for i.m. injections, nor is it unique to i.m. formulations. For example, Dr. Oleksowicz cites GnRH inhibitors as hormone therapies that were used at the time of the invention. Ex. 1004 at ¶ 43. One such GnRH inhibitor, goserelin, was approved in 1989 and is administered subcutaneously every 28 days. Ex. 2048 (Zoladex label) at 1.

158. Dr. Oleksowicz also states that "a POSA would understand that the typical route of administration in humans" for a steroid endocrine treatment "is by i.m. injection." Ex. 1004 at ¶ 170. But that is not necessarily true either as is demonstrated by high dose estrogen treatment (*e.g.*, ethinyl estradiol) and anti-progestogen agents (*e.g.*, mifepristone, onapristone) for breast cancer and oral birth control pills. Regardless, there is no "typical" route of administration for a steroid endocrine treatment.

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[6] The daily dose equivalent by weight of the other actives used in the study when compared to their clinical formulations are similarly striking (3,500 mg/day for letrozole; 291 mg/day for tamoxifen; 3,500 mg/day for 4-OHA).

159. McLeskey does not disclose plasma or blood levels of fulvestrant in mice after subcutaneous administration of any of the experimental drug formulations used. An ordinary researcher would not find the lack of pharmacokinetic data surprising given that the study was designed to look at issues relating to basic science and not drug formulation.

4) McLeskey Does Not Teach A Successful Fulvestrant Formulation

160. Dr. Oleksowicz claims that the fulvestrant formulations of McLeskey were successful treatments saying "McLeskey[], showed that in certain tamoxifen-resistant patients, an agent targeting the ER—such as fulvestrant—could theoretically be effective as second-line therapy." Ex. 1004 at ¶ 121.

161. The very text of McLeskey characterizes the fulvestrant animal formulations used as "**treatment failure[s]**." Ex. 1005 at 10. In fact, the very text of McLeskey repeatedly emphasizes the failure of these fulvestrant (ICI 182,780) animal formulations to arrest the cancer:

- "Treatment with ICI 182,780 ***did not inhibit*** tumor growth" (Ex. 1005 at 4);
- "***[F]ailure of ICI 182,780 to inhibit*** the estrogen-independent growth exhibited by this cell line" (*Id.*);
- "Fig. 1 Growth of FGF-transfected MCF-7 cells in ovariectomized nude mice is ***not inhibited by treatment with ICI 182,780***" (*Id.* at 5);

- "ICI 182,780 ***did not decrease tumor growth***" (*Id.*);
- "ICI 182,780 ***did not inhibit*** estrogen-independent tumor growth" (*Id.*);
- "Administration of ICI 182,780 to animals . . . ***produced no effect***" (*Id.*);
- "[T]he continued ***progressive in vivo growth***" (*Id.*);
- "Table 1 Metastasis of FGF-transfected MCF-7 cells is ***not inhibited by treatment with ICI 182,780*** or aromatase inhibitors" (*Id.* at 6);
- "Metastatic Frequency of Tumors Produced by FGF-transfected MCF-7 Cells in Mice Treated with ICI 182,780 or Aromatase Inhibitors Is ***Not Affected by Treatment***" (*Id.*);
- "FGF-transfected MCF-7 cells is ***not affected by ICI 182,780*** or by either of two aromatase inhibitors . . . treatment failure" (*Id.* at 10).

Even the title of McLeskey informs the skilled artisan that "Tamoxifen-resistant Fibroblast Growth Factor-transfected MCF-7 Cells Are Cross-Resistant *in Vivo* to the Antiestrogen ICI 182,780 [fulvestrant] and Two Aromatase Inhibitors." Ex. 1005 at 1. In other words, the cells are resistant to treatment with tamoxifen and additionally resistant to treatment by fulvestrant.

162. For this reason, McLeskey encourages the skilled artisan to seek alternatives to fulvestrant for breast cancer treatment. McLeskey explains that tamoxifen resistance is an "important therapeutic dilemma." Ex. 1005 at 1. The fact that the FGF-transfected cells were "cross-resistant" to the subsequent

exposure to endocrine agents indicates that none of the drugs (aromatase inhibitors or fulvestrant) used in the study worked to suppress tumor growth in this artificial model. For this reason alone a POSA would not recommend this formulation for human testing based on this study. Further, McLeskey cites the preliminary results in Howell 1995 and Howell 1996 for the proposition that many tamoxifen-resistant patients do not respond to fulvestrant. Ex. 1005 at 2. McLeskey proposed that the failure of tamoxifen-resistant patients to respond to further hormone therapy like fulvestrant suggests a hormone-independent mechanism of such resistance. Ex. 1005 at 2. McLeskey suggests that additional research should look to whether the growth factor, FGF, could provide such a hormone-independent mechanism.

163. McLeskey found that "[fulvestrant] did not affect the estrogen-independent growth of the FGF-transfected MCF-7 cells *in vivo*." Ex. 1005 at 6. McLeskey explained that "[t]hese studies indicate that estrogen independence may be achieved through FGF signaling pathways independent of ER pathways." Ex. 1005 at 1. McLeskey encouraged that, instead of using antiestrogen therapy, like fulvestrant, "[t]herapy of such tumors with agents directed against the autocrine or paracrine effects of FGFs might result in beneficial effects." Ex. 1005 at 12-13. McLeskey concluded that "[t]he persistence of estrogen-independent growth despite pharmacological strategies to abrogate all estrogenic activity supports the

hypothesis that the effect of FGF transfection in promoting such growth is due to a direct effect of the transfected FGF." Ex. 1005 at 10. Thus, McLeskey notes a problem with fulvestrant, proposes a mechanism to explain that problem, and reports experiments on the basic biology of such a hormone independent mechanism.

5) The Skilled Artisan Would Not Expect the Administration Method of McLeskey to Succeed

164. I completely disagree with Dr. Oleksowicz that "[k]nowing the exact fulvestrant formulation concentrations disclosed in McLeskey, a POSA would expect success in administering the formulation of fulvestrant to, at least, human females with HR+ breast cancer." Ex. 1004 at ¶ 168. It is not surprising that she provides no support for this statement in her declaration. Given that the fulvestrant formulations used in McLeskey were deemed a "treatment failure" when administered to mice, the ordinary researcher would certainly have no basis to expect success in administering those same formulations to humans using a different route and schedule of administration.

165. Moreover, McLeskey lacks any data from which an ordinary researcher could draw conclusions regarding drug absorption and metabolism, much less safety and efficacy. An ordinary researcher would not find the McLeskey reference description of any formulation to be helpful in looking to find a formulation to safely and effectively treat hormonal dependent diseases, such as breast cancer, in humans. Instead, the ordinary researcher reading

McLeskey would conclude that it raised doubts about the usefulness of anti-hormone treatments for breast cancer.

166. Mylan argues that "[a] POSA would have had a reasonable expectation that the castor-oil based formulation disclosed in McLeskey would have been effective for intramuscular administration to treat humans with hormonal diseases of the breast." Petition at 39. I disagree. McLeskey expressly states that both of the fulvestrant formulations used in the study were administered subcutaneously, not intramuscularly. There is no suggestion in McLeskey to administer the formulations intramuscularly. And, in fact, as discussed above, physicians consider intramuscular and subcutaneous administration to be very different because their environments for injection are entirely different. One could not extrapolate subcutaneous administration in mice to intramuscular administration in humans with any reasonable expectation of success, especially since the fulvestrant formulations in McLeskey "did not inhibit tumor growth." Ex. 1005 at 4 (emphasis added).

167. The results of McLeskey were characterized as a "failure" with regard to ICI 182,780. Ex. 1005 at 10. And, there is no information in McLeskey that indicates that ICI 182,780 was delivered to the blood plasma in any significant quantities.

168. Simply because live animals were used for the research does not make

the methodologies applicable for humans in the clinic. Much of basic biology research, being done on animals that will be sacrificed, is done using techniques and formulations not applicable to human treatment. For instance, as discussed above, the formulations used in McLeskey were laboratory formulations for use in basic biology research in animals: "[l]etrozole . . . was administered via gavage"; and "[s]ustained-release (60 day) pellets containing 5 mg of tamoxifen were obtained from Innovative Research of America." Ex. 1005 at 2. Moreover, the dose of "5 mg in 0.1 ml of vehicle every week" of fulvestrant would be equivalent to giving 12,000 mg per week to a human (based on weight), assuming that a mouse weighs 0.025 kg and a human weighs 60 kg (5 mg per week in mice * (60 kg human / 0.025 kg mice) = 12,000 mg), which would have been equivalent to giving 240 ml per week to a human. As noted above, a POSA would not look to a formulation such as McLeskey where 300 times the animal dose (which was identified as a "treatment failure") would be administered to humans and expect success.

B) Ground Two: McLeskey in Combination with Howell 1996

1) Howell 1996 Left Many Questions Unanswered And Was Questioned By Researchers At The Time

169. Dr. Oleksowicz argues that "Howell 1996 disclosed that the fulvestrant treatment was efficacious, well-tolerated, and achieved predicted therapeutic concentrations of fulvestrant for 1 month following a single

intramuscular injection." Ex. 1004 at ¶ 14. In my opinion, a skilled artisan would interpret the limited data in Howell 1995 and Howell 1996 with caution, and would not rely on these data to choose fulvestrant from the many other treatment candidates available at the time of the invention as it left many questions unanswered regarding active ingredient, amount, and route of administration.

170. Regarding active ingredient, Howell 1995 and Howell 1996 use data from the same underlying study of 19 "highly selected" patients (*i.e.*, patients most likely to respond to hormone treatment were selected for the study) by the same investigators, myself included. A skilled artisan would realize that the underlying study reported in these references was not from a large, randomized, double-blind Phase III clinical trial. It was a small, highly selected group of patients with hormone sensitive tumors and there was no control group comparing the results to the standard therapy at that time. And, indeed, we noted in Howell 1996 that the results needed to be confirmed in "future larger trials." Ex. 1006 at 6. A skilled artisan would interpret the results reported from this small non-randomized study with caution. In particular, the underlying study treated only 19 patients, administered a first dose of 100 mg to the first four patients for "appraisal of drug safety," did not have a placebo control, and was not blinded. Ex. 1006 at 2.

171. As noted in paragraph 74 above, up to one-third of responses could have been due to tamoxifen withdrawal. Therefore, the actual number of patients

whose tumors showed shrinkage based on treatment with fulvestrant may have been as low as 5 patients.

172. The skilled artisan would also be concerned about the possibility of fulvestrant resistance precluding further endocrine treatment and whether fulvestrant would have deleterious effects on other tissues and bone given its lack of estrogenic qualities. Ex. 1018 (Osborne 1995) at 5. For example, in Robertson 1997, which described the same 19-patient study of Howell 1996, we stated that "[n]one of the 10 patients who developed acquired resistance to [fulvestrant] subsequently showed an objective response to megestrol acetate as third-line therapy." Ex. 2041 (Robertson 1997) at 3. For this reason, we cautioned that "this early finding raises the hypothesis as to whether acquired resistance to [fulvestrant] may be equivalent to developing an endocrine resistant phenotype." Ex. 2041 (Robertson 1997) at 3.

173. Dr. Howell, himself, sounded a further note of caution based on the composition of the open label, phase II trial of 19 patients reported in Howell 1995, Howell 1996 and Robertson 1997. Referring to the Howell 1996 data, Dr. Howell wrote that "phase II studies are notoriously unreliable in predicting superiority over old agents." Ex. 2040 (Howell 1997) at 3-4. Thus, the authors of the phase II study of 19 patients highlight the limitations of the data and describe such data as "notoriously unreliable" in predicting whether a drug will successfully survive the

clinical development process.

174. Researchers at the time likewise suggested interpreting Howell 1995/1996 with caution. Ex. 2038 (Dowsett 1995) at 1 ("[T]he cited response rate of 13/9 (69%), albeit striking, should be interpreted with care in relation to other published data."). Those researchers also noted the highly selective nature of the patients studied in Howell 1995/1996 and that the approach taken in Howell 1995/1996 to include "no change" responses with objective responders is uncommon. Ex. 2038 (Dowsett 1995) at 1 ("First, although there are biological and clinical arguments to include patients with 6 months of no change with objective responders, this approach is uncommon. . . . Second, the group of patients that they selected for treatment would generally be regarded as favourable in relation to treatment with a second-line agent such as aromatase inhibitor.").

175. There are no details provided in Howell 1996 regarding the fulvestrant formulation used in that study other than that it was a monthly depot intramuscular injection of fulvestrant "contained in a castor oil-based vehicle" to 19 patients. Ex. 1006 at 2. Dr. Oleksowicz tries to suggest (without basis) that the McLeskey formulation and the Howell formulation were the same. In a related litigation, the defendants made the same allegations submitted by Mylan here, including just such an unsupported suggestion. The clinical expert testifying for those defendants, when questioned by the Court, admitted that a skilled artisan at the

time of the invention would have no idea what formulation was used in Howell 1996. He stated that any guess as to what formulation was used in that study would be "speculating," and that "[t]here is nothing in the literature to confirm [this] speculation." Ex. 2049 (July 14 Trial Tr.) at 213:10-17.

176. Regarding the amount of fulvestrant to deliver, a skilled artisan would need further experiments to determine the relationship between the responses observed in Howell 1996 and the reported blood plasma levels. In particular, the Howell 1996 paper stated that "a direct pharmacokinetic-pharmacodynamic link is not proven with the few patients studied to date." Ex. 1006 (Howell 1996) at 6. In fact, the paper goes on to say that "lower doses of the drug may be effective in maintaining therapeutic serum drug levels," but noted that "further clinical studies are required to confirm this hypothesis." Ex. 1006 at 6; *see also* Ex. 1006 at 7 ("At the dose used, there was accumulation of the drug over time and thus lower doses than those administered in this study may be as effective.").

177. In other words, while Howell 1996 initially targeted a blood plasma level between 2-3 ng/ml with 3 ng/ml set as a maximum blood plasma level, when analyzing the research results, Howell encouraged that further studies look to lower doses. Howell 1996 did not set a minimum blood plasma concentration of at least 2.5 ng/ml. And, because Howell 1996 suggested to go down in dose compared to that initial target, Howell 1996 even further taught away from

targeting at least 8.5 ng/ml as required by the claims.

178. For this reason, contrary to Dr. Oleksowicz's argument that "[i]t would be a routine and predictable method of optimization for a POSA to measure a patient's blood plasma fulvestrant concentration and to adjust the amount and frequency of fulvestrant administered to achieve concentrations at or above 8.5 $ngml^{-1}$ for 4 weeks," there would be no reason for a POSA to do so because the prior art suggested a lower dose. Ex. 1004 at ¶ 229. Her idea that it would be routine and predictable to optimize giving a formulation for a longer duration does not explain why a POSA would want to do so. It does not matter that a POSA could do it—there is no reason why a POSA would want to do it here especially in light of the art which suggested the opposite.

179. Lowering the dose was consistent with the knowledge from previous endocrine drugs at the time (*e.g.*, tamoxifen, toremifene, and anastrozole). For example, tamoxifen was studied in randomized clinical trials at doses of 40 mg and 20 mg, and it was determined that the higher dose did not confer any significant advantages over the lower 20 mg dose. Ex. 2050 (Bratherton) at 6 ("[N]o statistically significant advantage for 40mg daily over 20mg daily [tamoxifen] has been found[.]"); Ex. 2010 (Fornier) at 4 ("Several randomized studies demonstrated that tamoxifen doses higher than 20 mg/d do not confer further advantages."); Ex. 2014 (Pritchard 1997) at 7, 13 ("Several large randomized or

dose-finding studies have shown no major dose-response effect for doses of tamoxifen ranging from 2 to 100 mg/m^2 body surface area given twice daily. . . . Loading doses of tamoxifen had been suggested as being most consistent with its pharmacology but the lack of dose-response with the drug suggests that this approach is unlikely to be clinically useful."). Consequently, it is the lower dose of tamoxifen that is used in clinical practice.

180. Toremifene is another example of a SERM that showed no further clinical benefit with higher doses. Toremifene was investigated at doses of 200 mg and 60 mg and it was concluded that the higher dose provided no benefit over the lower dose and, in fact, may be associated with increased toxicity. Ex. 2010 (Fornier) at 4 ("Toremifene doses higher than 60 mg/d did not offer any advantages over lower doses."); Ex. 2016 (Buzdar Clin. Cancer Res. 1998) at 3 ("In a comparative trial involving women with advanced breast cancer, toremifene (60 and 200 mg) showed similar efficacy and safety to tamoxifen (20mg). The higher dose of toremifene had no benefit over the lower dose and was associated with an excess of liver function abnormalities; thus, 60 mg/day toremifene was approved for advanced breast cancer."); Ex. 2022 (Minton) at 2 ("To date, these phase III trials have not demonstrated greater benefit from higher doses of toremifene."). Toremifene was approved at the lower 60 mg dose.

181. The teaching of lower doses for endocrine agents similarly applied to

aromatase inhibitors. For example, anastrozole was studied clinically at two doses, 10 mg and 1 mg, and researchers concluded that there was no difference between the doses. Ex. 2010 (Fornier) at 4 ("No difference was found between the two doses [1mg v. 10 mg] of anastrozole."); Ex. 2022 (Minton) at 3 ("The group using 10 mg/day [of anastrozole] showed no advantage in response rate or survival over the group using 1 mg/day."). Anastrozole was approved at the lower 1 mg dose.

182. Thus, it was known at the time that for endocrine therapies higher tolerated doses did not improve efficacy. Ex. 2049 (July 14 Trial Tr.) at 216:4-11 ("Q. Dr. Mehta, you are familiar with the experience with endocrine therapies that greater doses even without toxicity did not lead to increased efficacy, right? A. I'm familiar with that. Q. And, for example, anastrozole was tolerated at 10 mg and 1 mg, but there is no additional clinical benefit for the higher dose, right? A. That is correct."), 219:15-20 ("Q. And, Dr. Mehta, you would agree that in fact anastrozole, aminoglutethimide and fadrozole studies all showed that higher tolerated doses did not provide greater efficacy? A. That is correct. Q. And all of that was known prior to 2000, correct? A. That is correct.").

183. In the phase III clinical trials of fulvestrant versus anastrozole, AstraZeneca included a lower dose of 125 mg, confirming that the skilled artisan would have sought lower blood plasma fulvestrant concentrations based on Howell 1996. This lower 125 mg dose of fulvestrant was subsequently not found to be

effective and was therefore dropped from both of these phase III trials of fulvestrant versus anastrozole. Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002).

184. Regarding route of administration, Howell 1996 would be recognized to be a preliminary study of safety and efficacy of the molecule in few patients. A skilled artisan would not conclude that even the method of administration used in Howell was optimal. Indeed, it is not unusual that the method of administration used in early phase clinical trials (first in man, or early Phase I or II studies) is not intended to be, or is discovered not to be, the best method of administration for clinical use. Ex. 2051 (Cohen) at 14; Ex. 2052 (Sweetana) at 9 (""Heroic' approaches describe efforts to solubilize drugs for early clinical studies [] using additives that probably are not acceptable for commercial formulations.").

185. Indeed, patients and physicians would also prefer an oral formulation. The leading SERM (tamoxifen) and aromatase inhibitor (anastrozole) were both administered orally. Then and even since, patients receiving endocrine therapy prefer to receive oral administration instead of injections. Ex. 2053 (Fallowfield 2006) at 1 ("Sixty-three per cent of patients preferred tablets, 24.5% preferred the injection and 12.5% had no preference."). In fact, "health-care professionals consider that patients dislike injections, and consequently they are more likely to prescribe oral treatments." Ex. 2053 (Fallowfield 2006) at 1.

186. Plus, the skilled artisan would have been concerned about the high

volume (5 ml) of the injection used in Howell 1996. Ex. 1006 at 2 ("i.m. injection (5 ml) into the buttock"). Prior to the invention of the '680 Patent, in the United States, 4 ml was believed to be the maximum recommended volume for intramuscular injection. Ex. 2054 (Beyea) at 1 ("For a large muscle such as the gluteus medius, use no more than 4 mL for adults and 1 to 2 mL for children and persons with less developed muscles."). Dr. Oleksowicz's statement that Howell 1995 buttresses her understanding that "Howell 1996 recognized that the 5 ml dose showed efficacy" and was well tolerated locally (Ex. 1004 at ¶¶ 204-205), once again, ignores that Howell 1995/1996 report on the same 19 patient study.

2) No Reason To Combine McLeskey With Howell 1996

187. Dr. Oleksowicz argues that "[a] POSA would furthermore understand that McLeskey's fulvestrant formulation could be useful for at least the treatment of human females with hormonal dependent breast cancer, as in Howell 1996." Ex. 1004 at ¶ 201. I strongly disagree. In addition to there being no reason to select either McLeskey or Howell 1996 as a starting point, as discussed above, one of ordinary skill would not have reasonably expected that animal research investigating a basic biological mechanism or creating a disease model for one biological (hormone independent, growth factor mediated) pathway (*i.e.*, FGF) could provide any relevant information regarding the usefulness of a specific pharmaceutical formulation for treating a disease in humans via a different

biological pathway (*i.e.*, ER). In my opinion, one of ordinary skill in the art would have had no reason to combine the basic biology rodent model research reported in McLeskey with the early stage clinical study reported in Howell 1996 and, he or she would not have had a reasonable expectation of success in doing so.

188. Dr. Oleksowicz argues that "a POSA would be aware of other fulvestrant or steroidal hormone formulations that were or could be 'long-acting,' i.m.-injectable, 'depot,' and/or contained in castor oil-based vehicles. One such publication was McLeskey." Ex. 1004 at ¶¶ 198-199. In other words, Dr. Oleksowicz suggests that McLeskey and Howell "match." They do not.[7]

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[7] First, this is misleading as McLeskey does not disclose a long-acting, i.m.-injectable, depot fulvestrant formulation. Second, this statement highlights Dr. Oleksowicz's retrospective analysis. By choosing McLeskey, which fails to teach nearly all of the limitations of the claims and itself describes the fulvestrant formulations used in the study as "treatment failure(s)," to combine with Howell 1996, Dr. Oleksowicz ignores the clear teachings of the art. Indeed, if a POSA were to look to any fulvestrant formulation based on Howell 1996, it would not look to a failed animal formulation such as the one disclosed in McLeskey but would instead look to other "potentially promising" fulvestrant formulations in the art (and cited by Howell) such as the castor-oil based formulation containing

189. As demonstrated in the table below, a researcher would have no motivation to combine the McLeskey formulation with the method described in Howell 1996 because the two simply do not match on nearly every significant parameter (other than active ingredient and vehicle).

Howell 1996	**McLeskey**
Intramuscular administration	Subcutaneous administration
To humans	To mice
Once monthly	Once weekly
250 mg/month dose in women	5 mg/week/mouse (0.025 kg) (5 mg/0.025 kg * 60 kg) **= 12,000 mg/week dose in women**
5 ml/month volume in women	0.1 ml/week/mouse (0.1 ml/0.025 kg * 60 kg) **= 240 ml/week volume in women**
Antitumor effects	Treatment failure

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benzyl alcohol in a dosage of 50mg-5g for intramuscular injection disclosed in Dukes 1989, which Dr. Oleksowicz herself admits "taught that anti-estrogens like fulvestrant were useful in treating post-menopausal symptoms." Ex. 1004 at ¶ 63; Ex. 1007 at 7.

Not cross resistant	Cross resistant

190. McLeskey studied a model of estrogen-independent growth, and not the claimed hormonal dependent breast cancer. Ex. 1005 at 2 ("We therefore sought to determine the sensitivity of the estrogen-independent tumor growth of FGF-transfected MCF-7 cells to [fulvestrant]."). McLeskey administered the castor oil-based formulation to cell cultures and mice, not humans. Ex. 1005 at 2. McLeskey administered the formulation subcutaneously, not by the claimed intramuscular route. Ex. 1005 at 2 ("ICI 182,780 . . . was administered s.c."). McLeskey administered the formulation weekly, not monthly or biweekly. Ex. 1005 at 2 ("ICI, 182,780 . . . was administered . . . every week."). McLeskey administered a dose of 5 mg/week per mouse, which is equivalent to 12,000 mg/week per woman (5 mg / 0.025 kg (weight of mouse) * 60 kg (weight of woman)). Ex. 1005 at 2. McLeskey administered 0.1 ml/week per mouse, which is equivalent to 240 ml/week per woman (0.1 ml / 0.025 (weight of mouse) * 60 kg (weight of woman)). Ex. 1005 at 2. The title of McLeskey declares that the tumors studied were "Cross-Resistant *in Vivo* to the Antiestrogen ICI 182,780." Ex. 1005 at 1. The abstract explains that the fulvestrant formulations "did not slow estrogen-independent growth or prevent metastasis of tumors produced by FGF-transfected MCF-7 cells in ovariectomized nude mice." Ex. 1005 at 1. And, McLeskey concluded that ICI 182,780 was a "treatment failure." Ex. 1005 at 10.

191. Moreover, in describing the rationale for the research, McLeskey cites to a range of eight papers reporting clinical study of fulvestrant and aromatase inhibitors and Howell 1996 is an author on four of the eight papers cited in that range, including one on aromatase inhibitors and one on endocrine therapies generally—there is no reason to pick out Howell 1996 as having some connection. If anything, McLeskey criticizes Howell 1996—as a rationale for the significance of her research relating to an alternative pathway, McLeskey interprets Howell 1996 as having a low percentage of positive responses to fulvestrant and aromatase inhibitors as support that a different, hormone-independent pathway exists. Ex. 1005 at 2 ("[E]arly results for small numbers of tamoxifen-resistant patients have shown that only about 30-40% of such patients have a positive response to subsequent ICI 182,780 or aromatase inhibitor therapy."). Further, the reasoning that McLeskey is somehow connected to AstraZeneca and that connects the animal research formulation to the Howell 1996 study is also attenuated. Other papers cited by Dr. Oleksowicz include the work of the AstraZeneca team, however, McLeskey has no AstraZeneca authors.

3) No Expectation That This Combination Would Successfully Treat Hormone Dependent Breast Cancer In Humans

192. A skilled artisan would also have no expectation that combining the formulation in McLeskey with the method in Howell 1996 would successfully treat postmenopausal women with hormone dependent breast cancer. First, as noted

above, the publications do not match on many significant parameters, each difference raising uncertainty. Second, each publication independently teaches away from the parameters of the claims. For example, Howell 1996 teaches a POSA to go down in dose (which turned out to be a failure). McLeskey refers to fulvestrant repeatedly as a treatment failure, cites to Howell 1996 as showing the low response rate of fulvestrant, and uses weekly subcutaneous administration. Third, as discussed in more detail below, many other promising drugs failed even after reaching late-stage clinical development so the limitations of both Howell 1996 and McLeskey noted above would provide no expectation of success to a clinician that the combination of the two could successfully treat hormone dependent breast cancer in postmenopausal women.

193. Dr. Oleksowicz's argument that "[a]lthough McLeskey administered her formulation of fulvestrant subcutaneously . . . when translating the treatment to a human, a POSA would expect to give a steroid hormone formulated in oil, and expect it to be long-acting, via intramuscular injection" ignores two important things: (1) there is no reason in either prior art reference to "translate" the McLeskey animal formulation to a human and (2) the fact that, as discussed above, one cannot simply extrapolate the results from subcutaneous administration in mice to intramuscular administration in humans and reasonably expect to achieve success in treating a female with hormone dependent breast cancer. Ex. 1004 at ¶

208. It is thus not surprising that the declaration does not provide any support for this statement.

194. Importantly, Dr. Oleksowicz provides no reason why a POSA would possibly expect the McLeskey fulvestrant formulations, which failed in animal experiments, to achieve success in humans using Howell 1996's method. As noted above, a POSA would not understand that "McLeskey's fulvestrant formulation could be useful for at least the treatment of human females with hormonal dependent breast cancer." Ex. 1004 at ¶ 201.

195. I disagree with Dr. Oleksowicz that Howell 1996 "confirmed the reliability of previous monkey studies, noting that the pharmacokinetic data in the post-menopausal human females were 'similar to those previously demonstrated in adult female monkeys'" and "a POSA would have expected fulvestrant to be safer than tamoxifen, in particular in minimizing development of uterine cancer, making fulvestrant a possible candidate to treat, at minimum, ER+ malignant diseases of female breast tissue." Ex. 1004 at ¶¶ 60, 124. These statements are baseless. Indeed, Howell explained that the previous monkey studies were not pharmacokinetically predicative -- they showed no accumulation while the humans in Howell showed accumulation. Many endocrine therapies, including SERMs, AIs, antiprogestins, and pure antiestrogens, produced encouraging pre-clinical and clinical results only to fail in later development.

196. Further, Dr. Oleksowicz argues that "[e]arly pre-clinical studies published in the 1990s demonstrated that fulvestrant's pure ER antagonist activity, together with its lack of significant uterotrophic (uterine and endometrial growth) effects, rendered it a 'prime candidate' for further development in patients with ER+ breast cancer." Ex. 1004 at ¶ 114. But, at the time of the invention leading to the '680 Patent, only a small number of innovator companies were pursuing pure antiestrogens. And, to date, no compound with the same mechanism of action as fulvestrant has ever received FDA approval. Simply because a compound shows promise in early clinical work does not provide a reasonable expectation that any method of treatment using that compound would be successful. Indeed, of the "promising" compounds described above, not one of the new compounds in development at the time reached the market except fulvestrant.

197. For example, the second-generation aromatase inhibitor formestane produced a 24% objective tumor response rate in a large clinical trial. Ex. 2025 (Masamura 1994) at 4. However, its intramuscular route of administration was considered an "[o]bstacle[] to the use of formestane." Ex. 2026 (Kelloff 1998) at 8. In particular, "studies reported sterile abscesses due to the intramuscular injection required for administration of this compound." Ex. 2026 (Masamura 1994) at 4. Formestane has not received FDA approval.

XIII) SECONDARY CONSIDERATIONS DEMONSTRATE THAT THE CLAIMED INVENTION IS NONOBVIOUS

A) Long-Felt Unmet Need

198. The invention method of treatment filled a long-felt need – *i.e.*, the need to improve on the current standard of care and also extend the sequence of endocrine therapies.

199. The invention method met a treatment need by improving clinical outcomes (*i.e.*, clinical benefit, time to progression, and overall survival benefits versus current standard of care). Ex. 2055 (Robertson 2009); Ex. 2056 (Robertson 2012); Ex. 2057 (Robertson SABCS 2014); Ex. 2058 (Ellis 2015).

200. From my clinical perspective, extending the period during which endocrine therapy can be used as an effective and viable treatment option for hormone dependent breast cancer is an important goal. While prior endocrine therapies had shown evidence of non-cross resistance, patients eventually became resistant to the subsequent endocrine treatment. Endocrine agents, which could show lack of cross-resistance with known endocrine agents and thereby could be used sequentially *before and after* other available therapies, are extremely valuable in extending the life of patients suffering with the disease. Ex. 2059 (Vergote 2003) at 4.

201. The invention method met a need for a new treatment that was not associated with cross-resistance to currently used endocrine therapies such as

tamoxifen or AIs or to subsequent endocrine therapies. Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002); Ex. 2060 (Robertson 2004); Ex. 2061 (Robertson Cancer 2003); Ex. 2062 (Chia 2008); Ex. 2063 (Johnston 2013); Ex. 2064 (Robertson 2005) at 1, 5 ("[P]ostmenopausal women with advanced breast cancer who respond to first-line fulvestrant or tamoxifen retain sensitivity to subsequent endocrine therapy. . . . [F]ulvestrant appears to offer an opportunity to prolong the time in which well-tolerated endocrine therapies are used before reliance upon cytotoxic chemotherapy is necessary."); Ex. 2065 (Johnston 2004) at 2 ("These results suggest that in addition to producing responses after prior tamoxifen, disease progression after anastrozole may not preclude subsequent treatment with fulvestrant.").

202. In addition to having sequential options, the FIRST and CONFIRM studies showed that putting Faslodex® (fulvestrant) intramuscular injection 500 mg into the sequence of treatment (whether in the first-line setting or second-line setting) provided not only an option in terms of cross-resistance but resulted in improved disease control and overall survival which satisfied an unmet need. In contrast, the introduction of nonsteroidal AIs, such as letrozole and anastrozole, into the sequence of endocrine therapies had not shown such improved disease control and improved overall survival in both the first and second-line setting. Anastrozole and letrozole were initially introduced in second-line based on reduced side effects (particularly weight gain) versus megestrol acetate. In the

first-line both anastrozole and letrozole showed improved disease control (*i.e.*, improved time to progression) but no significant difference in overall survival.

203. Indeed, it has been acknowledged in the literature that Faslodex® (fulvestrant) intramuscular injection met an unmet need. Ex. 2066 (Pharma Marketletter 2004) at 1-2 ("There has been an unmet need for an effective endocrine therapy which works in women who have become resistant to other hormonal treatments including tamoxifen and [AIs]. . . . [Faslodex® (fulvestrant) intramuscular injection] is a better treatment than other endocrine therapies and could be used in preference to [AIs] after tamoxifen or, eventually, even before tamoxifen."); Ex. 2067 (Cancer Weekly April 2004) at 2 (Faslodex® (fulvestrant) intramuscular injection was a new type of therapy which offered women with advanced breast cancer ("ABC") a method to "extend[] the sequence of 'patient-friendly' hormonal therapies that can be used to control the disease." The invention method "therefore [met] a key unmet need . . . since it c[ould] be added in to the sequence of well-tolerated hormonal therapies and may [have] delay[ed] the need to resort to cytotoxic chemotherapies with their well-recognized side effects.").

B) Unexpected Results

204. Based on the properties of the available hormone therapies, as well as the properties of fulvestrant itself, scientists and clinicians would not have expected the invention method to have its beneficial clinical results. The balance of side

effects and adverse events with efficacy (net clinical benefit) for the invention method would have been predicted to be similar or worse than the SERMs or AIs because fulvestrant, the active ingredient, acted, as those agents also do, on the estrogen pathway, and because it had no "balancing" agonist activity. For example, after the initial publication of the phase II trial of fulvestrant following progression on tamoxifen, scientists did not expect that a method of treatment using fulvestrant would be more effective than AIs or SERMs, noting that "[i]t remains to be seen whether it will be more effective than other non-steroidal anti-oestrogens with less agonist activity than tamoxifen or toremifene, such as idoxifene. Our data suggest that it may not be substantially more effective in terms of response rate than aromatase inhibitors, with which it is conceptually similar in its pure deprivation of the oestrogenic signal." Ex. 2038 (Dowsett 1995) at 1. A person of skill in the art would have expected the invention method to be cross-resistant with tamoxifen because both drugs prevent estrogen from binding to the ER (*i.e.*, ER antagonists). Ex. 2010 (Fornier) at 4; Ex. 2061 (Robertson Cancer 2003) at 2. At the time of the invention, it was known that other SERMs, which act on the ER, were cross-resistant with tamoxifen. Ex. 2010 (Fornier) at 4; Ex. 2013 (Johnston 1997) at 1; Ex. 2068 (Baumann 1998) at 1-2, 9; Ex. 2017 (Jordan 1995) at 1, 6-10; Ex. 2011 (Jordan Supp. 1995) at 2; Ex. 2069 (Pyrhönen 1994); Ex. 2070 (Stenbygaard 1993).

205. However, because of the unique combination of the active ingredient

and delivery system as well as the specific blood levels and profile achieved, the invention method surprisingly and unexpectedly showed improved clinical outcomes compared to AIs; and had an improved side effect profile compared to other hormone therapies (*e.g.*, antiestrogens, progestins).

1) Improved Clinical Outcomes

206. First, it was unexpected that the invention method would have improved clinical outcomes compared to AIs. AIs, "which block production of estrogen through their interaction with the estrogen-producing enzyme aromatase, [] demonstrated increased efficacy compared with the ER antagonist tamoxifen in postmenopausal women as first line endocrine treatment for ER+ advanced breast cancer and as adjuvant therapy for postmenopausal women with early breast cancer." Ex. 2071 (Robertson 2014) at 1.

207. Because fulvestrant, like tamoxifen, acts as an ER antagonist, a person of skill in the art would not have expected fulvestrant to be more efficacious than AIs. However, the invention method was unexpectedly more efficacious compared to AIs—particularly, a third-generation, gold standard AI, such as anastrozole.

208. For example, the 500 mg dose of the invention method displayed significantly longer time to progression (TTP) and treatment failure (TTF) and better overall survival (OS) compared with anastrozole 1 mg in the phase II FIRST trial. Ex. 2058 (Ellis 2015) at 3-6 ("This study reports improved OS with

fulvestrant 500 mg treatment compared with anastrozole in the first-line setting for ER-positive [ABC], with an approximately 30% reduction in mortality risk. . . . To our knowledge, this represents the first time an endocrine monotherapy has demonstrated improved efficacy compared with a third-generation AI."); Ex. 2057 (Robertson SABCS 2014) at 1 ("HR+ [patients] receiving first-line fulvestrant 500 mg lived significantly longer than [patients] on anastrozole . . . . FIRST is therefore the second randomized trial to show an OS advantage for fulvestrant 500 mg over another endocrine therapy."); Ex. 2071 (Robertson 2014) at 5 ("This was the first trial to indicate that an alternative endocrine therapy may be more effective than an AI in the first-line setting for [ABC.]"); Ex. 2072 (Barrios 2012) at 3 ("TTP was significantly prolonged with fulvestrant 500 mg [and d]ata from the FIRST study showed that the significant difference in TTP had persisted with longer follow-up[.]");Ex. 2056 (Robertson 2012) at 6 ("Fulvestrant 500 mg as first-line endocrine treatment was associated with a significantly longer TTP compared with anastrozole 1 mg . . . . [and] an improved TTF compared with anastrozole. . . . [M]edian TTF was significantly longer for fulvestrant versus anastrozole."); Ex. 2055 (Robertson 2009) at 4 ("[M]ost notably[,] median TTP [] was estimated to be 60% longer in patients treated with fulvestrant [high-dose (HD)] compared with TTP for those treated with anastrozole, a statistically significant difference."). In that same study, duration of response (DOR) and clinical benefit (DoCB) data

favored the 500 mg dose of the invention method versus anastrozole 1 mg, which supported "observations in previous fulvestrant studies suggesting that prolonged response may be a consistent benefit of fulvestrant treatment." Ex. 2055 (Robertson 2009) at 5.

209. With respect to the 250 mg dose of the invention method, "DOR was significantly longer for patients in the fulvestrant group compared with patients in the anastrozole group" in phase III trials comparing the 250 mg dose of the invention method and anastrozole 1 mg. Ex. 2061 (Robertson Cancer 2003) at 1, 7; Ex. 2073 (Robertson Eur. J. Cancer 2005) at 4 ("A combined analysis of all patients included in both second-line Phase III trials demonstrated a significant 30% increase in mean DOR in patients treated with fulvestrant."); Ex. 2074 (Clinical Practice Guidelines 2003) at 47 ("Fulvestrant [250 mg] appears to be at least as effective as anastrozole in patients whose disease progressed on previous endocrine therapy, and a recent reanalysis of these studies suggests a longer [DOR] favoring fulvestrant.").

2) Improved Side Effect Profile

210. The invention method had an unexpectedly better side-effect profile as compared with other hormonal agents. For example, as compared to AIs, the invention method was not associated with bone loss. Ex. 2075 (Vergote 2006) at 3 ("The AIs inhibit endogenous oestrogen synthesis via aromatase, which in

postmenopausal women results in very low plasma levels of oestrogen, and these agents may therefore be associated with some deleterious effects on bone."). A person of skill in the art would have "predicted undesirable action of pure antiestrogens in therapeutic use [due to a] tendency to reduce bone density and hence to precipitate or exacerbate osteoporosis." Ex. 1028 (Wakeling 1993) at 7. Faslodex® (fulvestrant) intramuscular injection is a pure antiestrogen but is not associated with bone loss (*i.e.*, there are no changes in serum markers of bone resorption or formation). Agrawal 2009 (Ex. 2076) reported on bone formation markers, bone alkaline phosphatase (BAP) and N- terminal propeptide of procollogen type 1 (PINP), and the bone resorption marker C-terminal telopeptide (CTX). Ex. 2076 (Agrawal 2009) at 3 ("[T]here was a lack of change in markers equating to long-term stability of bone turnover markers in postmenopausal women with [locally advanced primary breast cancer] treated with fulvestrant for over a period of 18 months. This is in contrast to the increase in bone markers (serum BAP, PINP and CTX) at 12 months compared to the baseline seen in 58 patients who received anastrozole in a sub-protocol study of patients in ATAC trial."). The absence of an effect of the invention method on these bone markers of resorption or formation was irrespective of dose for the 250 mg and 500 mg dose of the invention methods. Ex. 2077 (Kuter 2012) at 5 ("Serum bone marker levels were similar within and between the two groups throughout the study, with neither dose

producing substantial changes in any of the three bone markers assessed (ALP, CTX, and PINP)."). The use of the invention method avoids the bone loss which occurs with AI treatment. This was surprising because AIs have been known to cause bone loss and other skeletal-related events. Ex. 2078 (Buzdar 2006) at 5 ("Clinical trials including postmenopausal women with [early breast cancer] have confirmed that [AIs] have detrimental effects on bone, which may give rise to an increased risk of osteopenia, osteoporosis, and an increased susceptibility to fractures."). Moreover, "both steroidal and nonsteroidal [AIs have been] shown to increase markers of bone turnover." Ex. 2078 (Buzdar 2006) at 5 ("Anastrozole increased markers of bone resorption and formation in clinical studies, whereas letrozole increased bone resorption markers, but without a compensatory increase in bone formation markers. . . . [E]xemestane appears to increase both markers of formation and resorption to a greater extent than does either of the nonsteroidal agents.").

211. Surprisingly, the injections of the invention method are well tolerated locally, with a low incidence of injection-site reactions. Ex. 2075 (Vergote 2006) at 2 ("Fulvestrant i.m. injection was well tolerated locally; in most cases injection-site reactions were non-serious, mild and transient: only 4.6% and 1.1% of fulvestrant i.m. injections in trials 0021 and 0020, respectively resulted in injection-site events."); Ex. 2061 (Robertson Cancer 2003) at 9 ("The incidence of injection-site

reactions and withdrawals due to such reactions was low, indicating that administration of fulvestrant by injection is well tolerated and is not disadvantageous compared with oral administration."); Ex. 2028 (Howell 2002) at 6 ("Only 20 [fulvestrant] injections out of the total of 1,898 (1.1%) resulted in an injection site event."); Ex. 2029 (Osborne 2002) at 6 (finding that "86 fulvestrant courses (4.6%) of the total of 1,879 and 71 placebo courses (4.4%) of the total 1,624 resulted in an injection site event" which shows that fulvestrant doesn't cause injection site pain by itself and that the placebo (which used the same delivery system as that used for delivering fulvestrant) caused little injection-site reaction). This was surprising in and of itself because other injectable anticancer agents, such as the steroidal AI, formestane, were not well tolerated locally. Ex. 2075 (Vergote 2006) at 2 ("[F]ulvestrant i.m. injection is well tolerated [locally] in contrast to some other injectable anticancer agents such as the steroidal AI formestane."); Ex. 2025 (Masamura 1994) at 4 ("[S]tudies reported sterile abscesses due to the intramuscular injection required for administration of this compound [formestane]."). The local tolerance of the invention method permits divided dosing with two injections, allowing delivery of a 500 mg dose and the local tolerance of the injections permits long-term care.

212. The invention method therefore not only delivers fulvestrant in a manner that allows reproducible, prolonged release of fulvestrant which gives

stable drug exposure with blood concentrations maintained within a narrow range over 4 weeks but also produces very little injection-site reactions. Both were unexpected and the combination of the favorable absorption characteristics and the lack of local site reaction was even more unexpected.

C) The Invention Method Is The Reason For These Surprising Results

213. Treatment is a balance between side or adverse effects and beneficial efficacy effects. However, the pharmacodynamics for side or adverse effects may or may not be linearly linked. The blood plasma level profile of the drug impacts the correlation between side effects and beneficial effects.

214. The invention methods of the '680 Patent include concepts of a particular combination of ingredients to be administered in a particular way to achieve specific blood levels for treating a specific disease. The choice of active ingredient is but one part of treatment. An active ingredient alone cannot treat the disease -- it must be delivered in an effective, safe, and tolerable manner to the human body. Here, the entire invention method, including its delivery system leads to unexpected results of enhanced clinical benefit. The invention method can provide a sustained release of fulvestrant over one month, surprisingly achieving what had never been possible before (or since) with multiple dosing regimens of conventional dosage forms – the ability to attain higher blood levels and a reproducible blood plasma level profile and dose response, resulting in improved

efficacy and reduced side effects. As I noted after the large scale clinical testing of the invention method, it "offers the assurance of stable drug exposure, with plasma fulvestrant concentrations maintained within a narrow range throughout the administration interval," which minimizes the risk of drug-associated tolerance problems and "obviates patient compliance issues during long-term treatment." Ex. 2060 (Robertson 2004) at 10. The direct result of the invention method of treatment is an unexpectedly improved patient treatment. In fact, in the almost 30 years since the invention of the active ingredient, no other delivery mechanism has been invented that has been proven to effectively deliver fulvestrant safely and conveniently for long-term use.

215. The relationship between the invention method and its resulting steady blood plasma levels leading to the unexpected results of increased efficacy is demonstrated by the comparisons of results with two doses of Faslodex® (fulvestrant) intramuscular injection – 500 mg and 250 mg. The CONFIRM study (Faslodex® (fulvestrant) intramuscular injection 500 mg versus 250 mg) was carried out in the same advanced breast cancer population (*i.e.*, second-line endocrine therapy) as Studies 20 and 21 (Faslodex® (fulvestrant) intramuscular injection 250 mg versus anastrozole). Ex. 2004 (Di Leo 2010); Ex. 2005 (Di Leo 2014); Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002). Studies 20 and 21 both individually (Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002)) and when

combined (Ex. 2031 (Robertson Clin. Ther. 2003)) showed that 250 mg Faslodex® (fulvestrant) intramuscular injection in this patient population was equivalent to the third-generation aromatase inhibitor, anastrozole. The CONFIRM study carried out in a similar patient population then showed in a direct randomized comparison that Faslodex® (fulvestrant) intramuscular injection 500 mg was superior to 250 mg both in terms of time-to-progression and in terms of overall survival. Ex. 2004 (Di Leo 2010); Ex. 2005 (Di Leo 2014). An indirect comparison in the second-line setting indicates a benefit of the Faslodex® (fulvestrant) intramuscular injection 500 mg over anastrozole; these findings are consistent with the results of the direct comparison of Faslodex® (fulvestrant) intramuscular injection 500 mg versus anastrozole in the first-line setting reported in the FIRST study. Ex. 2055 (Robertson 2009); Ex. 2056 (Robertson 2012); Ex. 2057 (Robertson SABCS 2014); Ex. 2058 (Ellis 2015). Furthermore, the CONFIRM study shows that the higher dose of Faslodex® (fulvestrant) intramuscular injection (500 mg) with its increased concentration of fulvestrant compared to the 250 mg dose resulted in improved disease control on treatment, as shown by the improved progression-free-survival, and also improved overall survival. Ex. 2004 (Di Leo 2010); Ex. 2005 (Di Leo 2014). CONFIRM was a double-blind clinical trial comparing the same drug (Faslodex® (fulvestrant) intramuscular injection) at two different doses. There was therefore no need for the clinician or the patient to know which arm of the study the

patient was in when they had disease progression in terms of selecting subsequent therapy. Indeed, ~90% of patients in the CONFIRM trial were never unblinded in terms of what dose of Faslodex® (fulvestrant) intramuscular injection they had received. Since treatment options were therefore the same for patients in both arms of the trial following progression, the survival advantage seen in CONFIRM cannot be deemed to be due to differences in the treatment post-progression on fulvestrant. The improvement in disease control on treatment with the Faslodex® (fulvestrant) intramuscular injection 500 mg dose therefore appears to have carried through to result in an overall improvement in survival. The higher dose of Faslodex® (fulvestrant) intramuscular injection (500 mg) is linked to the higher serum concentration which, in turn, is linked directly to the formulation and method of treatment of the invention.

216. A person of skill in the art would have expected the 500 mg dose invention method to result in proportionally increased toxicity and adverse events as compared to the 250 mg dose invention method. However, the 500 mg dose invention method did not increase toxicity or safety concerns. Ex. 2004 (Di Leo 2010) at 1, 5; Ex. 2005 (Di Leo 2014) at 5; Ex. 2057 (Robertson SABCS 2014) at 1; Ex. 2071 (Robertson 2014) at 4; Ex. 2056 (Robertson 2012) at 2.

217. Compared to the 250 mg dose invention method, the 500 mg dose invention method results in increased down regulation in ER levels. The clinical

trial, NEWEST, found that "fulvestrant 500 mg is associated with significantly greater early reduction in tumor biomarker Ki67 and ER expression versus fulvestrant 250 mg." Ex. 2077 (Kuter 2012) at 8.

218. Additionally, two studies looking at the three dose regimes (approved dose ("AD"), loading dose ("LD"), high dose ("HD")) which, between them, were used in all of the clinical trials of Faslodex® (fulvestrant) intramuscular injection, were investigated in both an Asian population (Ex. 2006 (FINDER 1)) and a western population (Ex. 2007 (FINDER 2)) in 2010. Other than ethnicity, the demographics of the patients in both studies were similar. Plasma fulvestrant concentration level measurements including C_{max}, C_{min}, and AUC were in both studies approximately double for the Faslodex® (fulvestrant) intramuscular injection 500 mg dose compared to the 250 mg dose. Ex. 2006 (FINDER 1) at 2 ("[P]harmacokinetic (PK) analysis demonstrated that fulvestrant HD achieved plasma levels approximately double those seen with fulvestrant AD."); Ex. 2007 (FINDER 2) at 5, 7-8 ("At month 3, C_{min} and the AUC were similar for the AD and LD regimens, whereas these parameters were approximately doubled with the HD regimen. . . . While fulvestrant HD did not show superior efficacy versus fulvestrant AD in these two small Phase II studies, the CONFIRM study, which was a much larger, Phase III trial has clearly demonstrated the clinical benefits of fulvestrant HD over AD in the management

of postmenopausal women with advanced breast cancer."). Furthermore, FINDER 2 reports that "[r]ecent data from the large Phase III [CONFIRM] study, which compared the clinical benefit of fulvestrant HD versus AD in postmenopausal women with ER+ advanced breast cancer have shown that TTP was significantly longer for fulvestrant HD (n=362) than AD (n=374) (hazard ratio 0.80; 95% CI, 0.68, 0.94; P=0.006), corresponding to a 20% reduction in the risk of progression. Fulvestrant HD also showed numerical advantages in other secondary efficacy endpoints while keeping a similar tolerability profile to fulvestrant AD. Overall, these results suggest that the risk:benefit profile for fulvestrant HD is better than that of AD." Ex. 2007 (FINDER 2) at 7. The authors of FINDER 1 make a similar connection to the CONFIRM trial and conclude "[t]ogether with a favourable tolerability profile and no evidence of dose-related AEs, this equated to an improved benefit-risk profile for HD compared with AD." Ex. 2006 (FINDER 1) at 5. The patient demographics in the CONFIRM trial were similar to FINDERS 1 and 2, which all looked at second-line hormone therapy in patients with hormone receptor-positive metastatic breast cancer.

219. In contrast, increases in dose of other endocrine agents showed no corresponding increase in net clinical benefit, as discussed above at paragraphs 179-182.

220. The '680 Patent specification explicitly teaches the "therapeutically

significant levels," *i.e.*, the blood plasma levels that provide a therapeutic effect in a patient over the course of a month. Ex. 1001 at 9: 24-28. Furthermore, the specification teaches that the claimed method results in a "particularly even release profile with no evidence of precipitation of fulvestrant at the injection site." Ex. 1001 at 10:49-51. The unique characteristics of the method of the invention, as described above, have resulted in the improved clinical outcomes reported, for example, in the CONFIRM and the FIRST studies. Ex. 2004 (Di Leo 2010); Ex. 2005 (Di Leo 2014); Ex. 2055 (Robertson 2009); Ex. 2056 (Robertson 2012); Ex. 2057 (Robertson SABCS 2014); Ex. 2058 (Ellis 2015).

221. The PFS benefit found in the FIRST study has recently been shown through a phase III study. Specifically, an initial report of results of the FALCON study, a phase III trial directly comparing the 500 mg dose versus anastrozole, were published in a May 2016 press release. The purpose of the study was to demonstrate sufficient evidence that would change the standard of care in the first-line setting in patients with hormone dependent breast cancer. It was reported in the press release that the FALCON study met its primary end point of PFS which is a very important clinical finding. Ex. 2079 (FALCON Press Release). The full results of the FALCON study will be released in due course but these results demonstrate that AstraZeneca's clinical development of Faslodex® (fulvestrant) intramuscular injection continues to this day as we learn new and surprising information about this

drug.

222. By receiving FDA approval in 2002, Faslodex® (fulvestrant) injection became the first marketed pure antiestrogen, and none have been approved since.

XIV) CONCLUSION

223. Fulvestrant was a very difficult drug to formulate and administer according to the claimed method of treatment. It took eleven clinical trials and countless preclinical studies to discover the unique method of treatment claimed in the '680 Patent. The idea that any formulation, especially a formulation that was deemed a "treatment failure" by its authors, would work to achieve the long-lasting results contradicts the art and common sense.

224. For the foregoing reasons, it is my opinion that claims 1-20 of the '680 Patent are not obvious.

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

Dated: October 6, 2016

John F. R. Robertson, M.D.

EXHIBIT A

CURRICULUM VITAE

Professor John F.R. Robertson

INDEX

PERSONAL DETAILS

NAME	John Forsyth Russell Robertson
DATE OF BIRTH	20th February 1956
QUALIFICATIONS	M.B. Ch.B. (Glasgow) B.Sc. (Glasgow) F.R.C.S. (Glasgow) M.D. (Glasgow) Specialist Accreditation in General Surgery Cambridge Diploma in Religious Studies
FELLOWSHIP	Moynihan Travelling Fellowship

APPOINTMENTS

August 11 -	Professor of Surgery based at the Royal Derby Hospital, Derby
Aug 98 – July 11	Professor of Surgery based at the City Hospital, Nottingham
Aug 96 - July 98	Reader in Surgery (Honorary Consultant Surgeon) based at the City Hospital, Nottingham
June 92 - July 96	Senior Lecturer in Surgery (Honorary Consultant Surgeon) based at the City Hospital, Nottingham

CLINICAL EXPERIENCE

i) Breast Surgery

Over the last 32 years I have acquired extensive clinical experience in breast disease. I am Professor of Breast Surgery at the University of Nottingham, based at the Royal Derby Hospital, Derby. The Breast Unit has a multi-disciplinary team which looks after patients from high risk/prevention through screening, symptomatic primary breast cancer, locally advanced and metastatic disease to terminal care. I have clinical experience in all these areas.

Prior to moving to Derby in 2011 the academic unit was based at the City Hospital, Nottingham which also has a large Breast Unit seeing approximately 6,000 new breast referrals, and treated between 500 - 600 new breast cancer patients, each year. This number of patients allowed us to run clinics for specific conditions - e.g. benign breast pain, benign breast lumps, family history, primary operable breast cancer, locally advanced breast cancer, elderly primary breast cancer and systemically advanced breast cancer. These specialist clinics formed the basis for much of the clinical research programme and is the model we are further developing at Royal Derby Hospital.

With regard to surgery for operable breast cancer I perform conservation surgery or mastectomy as appropriate. I was responsible for establishing a joint reconstructive service between breast and plastic surgeons in Nottingham in 1992, which was one of the first in the UK, offering a full range of breast reconstruction techniques in a multi-disciplinary approach. Our research interest in developing a blood test for early detection has meant we have a particular focus on early stage disease. Nevertheless one of my major clinical (and research) interests has been (and remains) advanced breast cancer – both locally advanced and metastatic disease, which I jointly run with my clinical oncology colleagues. As a surgical oncologist with both a major clinical and laboratory interest in endocrine and growth factor therapies I find myself in a central position – e.g. able to provide a link between surgical and non-surgical (clinical and medical) oncologists which ensures seamless continuity of care for patients and a rich base from which clinical and laboratory research can proceed. The Department's interest in systemic therapies has placed it

as one the vanguard of surgical units performing pre-surgical ('window of opportunity') studies which allows us to combine our skillsets in surgery and systemic therapies into a translational research programme investigating biological changes in breast cancers which matches our therapeutic clinical trials in advanced disease. I am currently one of the three Chief Investigators (CIs) on the POETIC trial which is the largest trial of peri-operative endocrine therapy in the world. I am also the CI of the STAKT trial, which is the first pre-surgical study under the AstraZeneca-NCRN concordat: this is a dose ranging study of an AKT inhibitor, AZD5363. I have been CI, or local Principal Investigator (PI), in a number of multicenter trials for new drugs produced by a variety of pharmaceutical companies including Astrazeneca, Novartis, Amgen, Schering, and Bayer.

ii) General Surgery

I trained and worked as a General Surgeon for almost 30 years. During my first 10 years as a Consultant Surgeon I was routinely looking after, and operating on, patients with gastro-intestinal (GI) problems, especially gastric and colorectal cancers, as well as breast cancer. With the introduction of site-specialisation following the Calman-Hine Report the treatment of GI tumours was taken over by site-specific teams. Following this my general surgical work decreased and after 18 years I came off the emergency general surgical rota. However my training and initial involvement in the treatment of GI cancers gave me experience of a wide spectrum of solid tumour types.

TEACHING

1. Departmental

i) Clinical

The University of Nottingham has a systems based undergraduate curriculum. I was involved in implementing the undergraduate curriculum at the City Hospital when it was re-designed some years ago. I was particularly involved in teaching the subjects of breast cancer and gastrointestinal malignancies. For three years I also had responsibility for the MCQs for the Final Year MCQ paper. I then took on responsibility

for a Special Study module based around 'Female Cancers' which I subsequently passed on to one of the Associate Professors in my Department.

I also have experience of organising Teaching Courses on Counselling and Communication Skills both for undergraduate medical students and postgraduate junior surgical staff. The students' assessment of these teaching courses was carried out by the external facilitator. These courses were subsequently incorporated by the post-graduate tutor at the City Hospital into a plan for similar courses for medical staff. I sat on the initial Steering Committee for this programme.

ii) Supervision of Research

I have supervised a number of under- and post-graduate medical trainees and non-clinical scientists over the years. For example over the last five years I have had seven physicians presenting themselves for post-graduate MD degrees, seven scientists presenting for PhDs one M. Phil and five MSc students.
They have been involved in translational research work in the areas of endocrine and growth factor therapies and serum tumour markers in breast cancer.

2. Other teaching commitment:

The Nottingham Breast Cancer Screening Unit is one of the four national screening teaching centres. I was one of the faculty of speakers for the Nottingham Breast Cancer Screening Training Programmes which include a multi-disciplinary course twice per year on breast screening as well as regular one day update seminars and workshops.

The British Association of Surgical Oncology (BASO) and the Royal College of Surgeons of England jointly host an advanced course on "The Management of Breast Disease". This was a week-long course for senior surgical trainees and consultants with a special interest in breast disease. I was one of the original teaching faculty on this course being responsible for the section in the course on advanced breast cancer. I have

been a teacher on the Breast Disease section of the local FRCS course and have also previously examined for the FRCS (Glasgow) examination.

I have organised two, and three, day Oncology Training Programmes focused primarily on breast cancer. These courses have run regularly two or three times a year, for 20 years (since 1993). I have delivered training on endocrine therapies to over 175 breast cancer oncologists who have travelled from over 40 countries to attend training courses since 2008 at the University of Nottingham. I have also been an invited speaker on endocrine therapy and growth factor therapies at over 50 international breast cancer meetings covering six continents since 2008. For five years (1994-99) I organised regular specialist Workshops on Serum Tumour Markers in Breast Cancer under the auspices of the European Group for Serum Tumour Markers in Breast Cancer. I have previously organized a symposium on the Design and Analysis of Clinical Trials, run jointly under the University Departments of Surgery and Epidemiology and Public Health.

MD Thesis

"New criteria for assessment of response in systemic breast cancer"

My post-graduate thesis examined the role of tumour markers in breast cancer and was awarded the degree of M.D by the University of Glasgow. This study identified a biochemical serum measurement of tumour mass and of response to endocrine therapy in systemic breast cancer which is objective, reproducible, gives an early result and can therefore be used in monitoring therapy and should replace the UICC criteria for comparing response rates.

The biochemical index established in my thesis has been confirmed both in our own centre and in a European multicentre study. This was the catalyst for the programme of research on autoantibodies in cancer which has resulted to the first blood test for early detection of lung cancer based on detection of autoantibodies to cancer antigens in a blood sample – the EarlyCDT-Lung test.

RESEARCH EXPERIENCE

Breast Cancer - Breast cancer has been my major research interest over 28 years. Throughout this period I have focused my research in two main areas: endocrine and growth factor therapies and serum tumour markers.

Endocrine Therapy - my research in this field has focused on the following areas:

i) Clinical studies of endocrine therapy

Summary - I have experience in running clinical studies investigating all the major classes of endocrine therapy and more recently investigating growth factor therapies. I have been CI of national and international multi-centre trials of both endocrine and growth factor therapies. I have been a leading international investigator on fulvestrant (Faslodex): the only new endocrine therapy for breast cancer registered worldwide in last 10 yrs. I have participated in 13 clinical studies involving fulvestrant and was CI in nine of these (7/9 were multi-centre RCTs – 3 UK and 4 international), more than any other clinical academic worldwide.

Details - I have overseen a number of clinical studies on the role of endocrine therapy in patients with different stages of disease.

In primary breast cancer these have included the following randomized clinical trials (RCTs):-

a) Tamoxifen versus mastectomy in elderly patients with primary operable breast cancer (unselected for ER),

b) Tamoxifen versus Tamoxifen and mastectomy in patients with highly positive ER tumours,

c) Tamoxifen versus radical radiotherapy in patients with locally advanced breast cancer

d) Tamoxifen versus multiple modality treatment (neoadjuvant chemotherapy, mastectomy, radiotherapy and endocrine therapy) again in patients with locally advanced primary tumours.

e) v) POETIC - Trial of Perioperative Endocrine Therapy - Individualising Care – to assess if 4 weeks of an aromat6ase inhibitor can affect long term outcome. (one of 3 CIs: UK multi-centre RCT)

In advanced breast cancer I have been the local PI on many international Phase 2 and/or 3 studies of all classes of endocrine agent. In a number of these RCTs my contribution to these studies overall has led to me being first, second or senior author on the study publication.

I have also been CI on a number of multi-centre phase 2 and 3 studies of endocrine and growth factor therapies. Studies I have been CI on include:-

a) Onapristone study – Phase 2 study of a new progesterone receptor antagonist in hormone naïve post-menopausal women with advance breast cancer (CI: Single centre study)
b) Study 59 – dose and pharmacokinetic study of fulvestrant in post-menopausal patients with advanced breast cancer (CI: UK multi-centre RCT)
c) Study 003 – Phase 2 study of gefitinib (EFGR tyrosine kinase inhibitor) in patients with either (i) tamoxifen resistant ER positive tumours or (ii) ER negative tumours. (CI: UK single centre study)
d) FIRST study – Phase 2 RCT comparing fulvestrant 500mg versus anastrozole in hormone naïve patients with advanced breast cancer (CI: international multi-centre RCT)
e) FALCON study Phase 3 RCT comparing fulvestrant 500mg versus anastrozole in hormone naïve patients with advanced breast cancer (CI: international multi-centre RCT)
f) GAMG 362 study – RCT looking at and anti-IGFR monoclonal antibody therapy in endocrine resistant advanced breast cancer (CI: international multi-centre RCT)

I have been involved in clinical studies from prevention (e.g. IBIS 1 and 2) through to metastatic disease and have investigated all major types of endocrine agents (e.g. GnRH agonists (goserelin), SERMs (tamoxifen), aromatase inhibitors, pure ER antagonists, PR antagonists). I have also been CI of a number of investigator initiated phase II studies of endocrine therapies and new growth factor therapies (e.g. gefitinib, IGFR monoclonal antibody therapy). A number of these studies have been focused on serum and tumour biopsies as a means of understanding the effects of these drugs on endocrine

resistance. I have also been local PI as part of a number of other multi-centre clinical trials of new agents such as mTOR and Pi3Kinase inhibitors.

ii) Factors predicting response of breast cancer to endocrine therapy

Summary - This has been one of the long-term areas of collaborative research between the Department of Surgery and Tenovus Institute, Cardiff. This programme has examined clinical and biological factors as predictors of de-novo response/resistance and also acquired resistance to endocrine therapy.

Details - These studies have included investigation of both clinical factors (e.g. patient age, site of disease) and tumour biology (e.g. ER, PgR, pS2, EGFR, TGFalpha, HER-2, IGFR1, AKT, MAPK, Ki 67) and the interactions between these factors and response to the Selective Estrogen Receptor Modulator (SERM), tamoxifen and the Selective Estrogen Receptor Down-regulator (SERD), fulvestrant. ER still appears the best single factor in that ER negativity is a powerful predictor of de-novo resistance. However thirty percent of ER positive tumours do not respond to initial endocrine therapy and we initially identified that these tend to show a combined phenotype of weak/moderate ER expression along with high expression of the proliferation antigen Ki67. Since then we have published extensively on other biological factors in the untreated primary tumour which predict for de-novo resistance. We have, however, been unable to identify biological markers in the primary tumour which predict for acquired resistance in each individual patient. This therefore led us into studies of sequential biopsies to look at changes in breast tumour biology which may be associated with acquired endocrine resistance. We are also one of the few groups who have investigated biological factors and response to second-line endocrine therapy.

iii) The effect of endocrine and growth factor therapies on the biology of invasive breast cancers

Summary - Sequential biopsies of breast tumours pre-treatment and during endocrine therapies have allowed us to study the effect of different endocrine and growth factor therapies on the biology of human breast cancers.

Details – It was in 1987 that I initiated one of the first studies in our unit looking at the effect of endocrine therapy (Tamoxifen) on breast tumours – an area which is now called 'translational research'. Following publication of the results of the study this area of our research was expanded and became a major part of the joint Nottingham/Tenovus Breast Cancer Programme. The research has assessed the effects on sequential biopsies of human primary breast tumours of a number of agents, including tamoxifen, gamma linoleic acid, aromatase inhibitors, fulvestrant, gefitinib and the pure anti-progesterone, onapristone. These sequential biopsies have been analysed for markers of tumour differentiation, programmed cell death, proliferation, growth factors and their receptors (particularly tyrosine kinase mediated receptors), markers of endocrine resistance (e.g. AKT, ras) and also a number of oestrogen inducible genes and their respective proteins.

A separate series of sequential biopsy studies have been short term treatment (<3 weeks) in the pre-surgical setting. I have been CI in the following pre and peri-operative RCT studies:

a) Pre-surgical treatment comparing the biological effects of fulvestrant (25, 125 and 250mg) versus tamoxifen 20mg versus placebo in post-menopausal patients (CI: UK multi-centre RCT)
b) Pre-surgical treatment comparing the biological effects of fulvestrant 250mg versus placebo in pre-menopausal patients (CI: international multi-centre RCT)
c) Pre-surgical treatment comparing the biological effects of fulvestrant 500mg versus anastrozole versus fulvestrant 500mg + anastrozole. (CI: UK multi-centre RCT)
d) POETIC - Trial of Perioperative Endocrine Therapy - Individualising Care – to assess if four weeks of an aromat6ase inhibitor can affect long term outcome. (one of three CIs: UK multi-centre RCT)
e) STAKT trial – dose ranging study of a new AKT inhibitor (AZD5363) (CI: UK multi-centre RCT)

iv) Oestrogen receptor and endocrine therapy

Summary - Oestrogen receptor (ER) has been linked to both primary and acquired endocrine resistance. While ER undoubtedly plays a part in acquired resistance it appears to be not the sole or possibly even not the most important cause of acquired resistance.

Details - ER is currently the most generally used predictor of response to endocrine therapy. In the early 1990s it was proposed that that loss of ER was a major mechanism of acquired endocrine resistance. I proposed a contrary view that ER is a stable phenotype in breast cancer which was published in the British Journal of Cancer in 1996 (REF 91). This is based on (i) review of the literature, (ii) unpublished data from our own laboratories showing ER in breast tumours at the time of acquired resistance and (iii) a clinical study which we had just published in which tumours post-tamoxifen responded to the specific anti-oestrogen ICI 182,780 implying ER was still functional. Today most experts believe that while a minority of tumours (probably <10%) do seem to lose ER expression the majority of acquired resistance is caused through other mechanisms such as 'cross-talk'. We have ongoing studies investigating alternative mechanisms for acquired resistance-e.g. type 1 or insulin-like growth factor pathways, AKT pathway. Pre-surgical studies have provided opportunities to look at short term effects of these drugs on different cellular pathways.

v) Progesterone receptor antagonists in breast cancer

Summary - This is a new class of compound which we have shown is an effective endocrine agent. The biological effects are different from current anti-oestrogen agents.

Details - I was the PI of a phase II study of Onapristone (Type 1 PgR antagonist) in patients with locally advanced breast cancer. This study showed Onapristone was an effective endocrine therapy. During treatment we also obtained sequential biopsies of these human tumours. The development of Onapristone was discontinued due to transient liver function test (LFT) abnormalities I identified. Subsequently (e.g. ten years later), a second generation progesterone receptor antagonist was available. A Phase 2 study of lonaprisan (type 3 PgR antagonist) has recently published lack of efficacy of this endocrine agent. Future research looks to be focused on alternative anti-progesterone antagonists (e.g. non-steroidal agents) or better selection for Onapristone such that the therapeutic benefits outweigh the potential risks of transient LFT abnormalities.

vi) Specific calmodulin antagonists with no anti-oestrogenic action

Summary - We developed a programme to investigate whether such compounds (i) inhibit tumours resistant de-novo to anti-oestrogen (tamoxifen) therapy and/or (ii) are additive or synergistic with established endocrine agents in hormone sensitive tumours.

Details - I carried out a pilot study in our laboratories in collaboration with Nottingham Trent University on the effect of specific calmodulin antagonists in breast cancer cell lines. There appears to have been no systematic attempt to develop non-oestrogenic calmodulin inhibitors as anti-proliferative agents. Endocrine agents such as tamoxifen and idoxifene possess both anti-oestrogenic properties and inhibit calmodulin. A series of calmodulin inhibitors related to W-7 with no anti-oestrogenic activity was developed which in pilot experiments were shown to be potent anti-proliferative agents. Unfortunately funding to further develop this programme was not secured and it was therefore discontinued. However calmodulin antagonists have recently become a focus for new drug development.

Serum tumour markers

i) Laboratory research on established markers

Summary - I established a biochemical index combining three serum tumour markers for use in measuring response in patients with metastatic breast cancer.

Details - My interest in serum tumour markers started with my MD thesis which investigated the role of serum markers in the assessment of therapeutic response to endocrine therapy in patients with advanced breast cancer. In patients with metastases the pre-treatment level of serum markers was of no value in predicting subsequent therapeutic response. However, changes in concentration of serum markers did provide an early measure of subsequent therapeutic response to endocrine therapy. Subsequent studies have shown that changes in these serum markers also measure therapeutic response to chemotherapy.
We then set up a multi-centre European study involving 11 centres in six EU countries for which I was the PI. This confirmed, in a European multicentre setting, the use of the biochemical index in measuring

therapeutic response, which in fact in many patients identified response and progression before imaging tests (e.g. CT, ultrasound). The pilot study was in preparation for a randomised clinical trial comparing serum tumour markers versus standard response assessment criteria (UICC) but we were unable to secure funding for the randomized controlled trial.

We also set up a clinical study assessing the use of blood tumour markers in the disease-free interval follow-up of patients treated for primary breast cancer. This study was set up to assess the lead-time provided by tumour markers in diagnosis of recurrence and also to estimate the cost-effectiveness of this form of follow-up. The study was set up so that it would, in due course, lead to a multi-centre study to test the concept of early therapeutic intervention based on sequential blood marker measurements.

ii) New markers in advanced disease

Summary - We have investigated a number of new blood tumour markers for metastatic disease.

Detail - We instigated a laboratory project looking for new serum markers of tumour proliferation (e.g. thymidine kinase, tissue polypeptide specific antigen), apoptosis and oestrogen regulated markers (e.g. c-erbB-2) which might provide additional information to current markers which reflect tumour bulk. None appeared to add anything to the established markers. An interesting result of this work was the unexpected finding that serum HER2 expression is prognostic of patient outcome (e.g. survival) at all stages of breast cancer. This may be related to the well-established fact that tissue expression of HER2 is also of prognostic significance.

iii) Development of "near patient" assays

We completed a collaborative study to assess whether the current commercially available assays could be compressed thereby making it possible to produce serum marker results for patients during their outpatient visit. Unfortunately this was not possible with the assays tested.

iv) Other research in breast cancer

I have substantial experience in investigating prognostic factors in locally and systemically advanced breast cancer as well as the area of primary disease for which the Nottingham Breast Unit is widely known for the 'Nottingham Prognostic Index' (NPI).

I initiated studies to define optimal treatment for elderly patients with breast cancer - work which has been taken up and developed by an Associate Professor in my department.

Surgical oncology

Summary - In other cancers (e.g. gastrointestinal) I concentrated my research on endocrine therapy and tumour markers, thereby linking it to my main research interests in breast cancer.

Details - I have had other oncology research interests - principally the gastro-intestinal tract. I have had both laboratory and clinical projects on hormone receptors and on the role of hormones and growth factors in gastrointestinal cancer. A post-graduate scientist completed a research programme under my direction assessing the value of sex steroid hormones in GI tumours. I have also previously been involved in research on the role of GI peptide hormones in gastrointestinal tumours. I have also carried out studies assessing the role of serum tumour markers (e.g. CA19-9, thymidine kinase) in gastrointestinal malignancies.

Screening

Summary - I was exposed to 3 screening programmes (for breast, colorectal and gastric cancers) during my surgical training. Subsequently I have been involved in breast screening for 26 years. More recently I have been involved in the developing programmes for lung cancer screening, the latter in relation to our blood test for early detection (see below).

Nottingham is a National Breast Screening Training Centre. We had an ongoing research programme focused on the radiology, pathology and treatment of screen detected cancers compared with symptomatic breast cancers. These studies were carried out in collaboration between the different disciplines.

CURRENT RESEARCH

The focus of my current research is on endocrine and growth factor therapies in breast cancer and serum tumour markers.

Endocrine Therapy in Breast Cancer

i. Clinical and Translational research

Summary - We plan to extend our research programme looking at a) tumour biology as a predictor of outcome on subsequent endocrine therapy, b) the effect of different endocrine and growth factor therapies on tumour biology.

Details - We have constructed a large database of over 500 patients treated with endocrine therapy on whom we have samples (tumour tissue and/or serum) and clinical data. This forms the basis for our studies to investigate the interactions between markers of oestrogen mediated pathways (ER, PgR, pS2) and growth factors (such as EGFR, HER2, HER3 TGFalpha, TGFbeta, IGFR1, MAPK, AKT, etc). Previous studies including our own have had too few patients to investigate subpopulations particularly ones such as ER positive, primary endocrine resistant tumours where, despite the presence of ER, other non-oestrogenic factors appear to control cell proliferation.

I also have a collection of sequential tumour biopsy and serum samples from patients on different types of endocrine and growth factor therapies. These involve breast tumours which were biopsied pre-treatment, while it was in response and which have then subsequently developed acquired resistance. It takes a long time and painstaking clinical research to accrue sufficient numbers of these particular specimens. However such biopsies have the potential to provide important insights into the mechanisms of acquired endocrine resistance and how this may be circumvented. These studies form a significant part of the continuing joint Nottingham/Derby/Tenovus Research Programme.

In the last five years I have been PI on early Phase 2 studies of four new drugs and PI of two international and two UK multicentre studies. I am currently one of the two CIs on a new Phase 3 RCT in first line metastatic disease comparing fulvestrant 500mg versus anastrozole. I am also CI of a multi-centre RCT assessing different doses of an AKT inhibitor in a pre-surgical study.

ii. Laboratory studies

Summary – I currently have an ongoing laboratory research programme with the Tenovus Institute in Cardiff investigating factors involved in acquired endocrine resistance.

Details - A significant part of my research in this area continues to be carried out in collaboration with the Tenovus Institute, Cardiff. In these studies we are interested in the expression of oestrogen regulated genes, and intracellular signaling pathways in-vitro cell culture and in-vivo models. The in-vitro and in-vivo effects inform our research on human tumour biopsy samples, especially where tissue is valuable such as in the sequential core biopsy studies. We have previously reported on the importance of type 1 growth factor pathway markers (e.g. EGFR, HER2, HER3, MAPK, etc) and insulin-like growth factor pathway markers (e.g. IGFR1, IR, etc). One of our current research interests is looking at the PI3Kinase and AKT pathway in relation to hormone resistance.

SERUM MARKERS

Serum Markers in Breast Cancer

i) Clinical

We established a multicentre study on the use of blood markers in monitoring disease recurrence after primary surgery. This study has collected blood samples for between 5-10 years while the clinical follow-up data was collected as part of the ATAC trial. The collection of samples is now completed and we plan to measure both antigen-based tumour associated markers and more novel markers such as auto antibodies to assess whether or not any rise in the markers measured will correlate with those patients who subsequently show overt metastatic disease. It is envisaged that the results from this study will lead to a subsequent

randomised study of early therapeutic intervention based on rising markers versus standard follow-up which we have called the SATS study (Secondary Adjuvant Therapy Study).

ii) Laboratory studies

In 1996 I established a small laboratory programme to identify new serum tumour markers for screening and early detection of primary breast cancer. The project was focused on the use of molecular technologies to try and amplify signals/markers of early carcinogenesis. Initially we investigated both ex-vivo amplification (using PCR techniques) and in-vivo amplification signal (by measuring autoantibodies to cancer associated antigens). In the first instance the auto-antibodies detected in the peripheral blood of patients with primary disease were to markers such as MUC1 mucin, p53, c-erbB2 and c-myc. The assays for these markers, along with a number of new markers were developed in our laboratories. We also developed a focus on lung cancer through an EU grant.

The autoantibody technology we developed was placed in a University of Nottingham spinout company, Oncimmune (see below) for commercialization while the academic department continued its research in lung cancer, breast cancer and more recently hepatocellular and colon cancer. As a result of this work the University has created the Centre of Excellence for Autoimmunity in Cancer (CEAC) of which I am the Director (http://www.nottingham.ac.uk/ceac).

CEAC

There is an urgent need for new, more effective and more patient-acceptable screening tests for most types of cancer. We believe our research team is one of a very few, if not the only one, in the world currently able to deliver blood based screening tests based on autoantibody technology for all types of solid cancers. This programme is very ambitious in its goal, but justifiable, given The University of Nottingham's experience in delivering the world first autoantibody blood test for lung cancer, EarlyCDT-Lung. Establishing a programme to assess the value of a wide range of Tumour-Associated Antigens (TAAs) and how each relates to a different type of tumours will be crucial in the development of tests for each type of cancer. We now have

MRC funding to support research projects looking at autoantibodies to tumour antigens as early detection tests for colon, pancreatic and hepatocellular cancers.

In addition to developing new tests we have established a number of international collaborations to investigate, for example, i) how early pre-diagnosis of cancer the autoantibody signal can be detected, ii) are there autoantibodies to cancer stem cells, iii) the value of the autoantibody signal in relation to differentiating benign and malignant lung nodules, iv) understanding the biology of early carcinogenesis. These collaborations include centres in North America (e.g. British Columbia Cancer Centre in Vancouver, Vanderbilt University, Mayo Clinic, National Jewish Hospital in Colorado) and Europe (e.g. Munich, Trondheim, Malmo, Milan, Navarra). We also have approval to access two lung cancer screening study sample banks (PLCO and NLST – both NIH funded RCTs).

SPINOUT COMPANIES

I have started three spinout companies from my research work:-

i) Oncimmune

Oncimmune is a spinout company from the University of Nottingham which has developed the autoantibody technology and IP which came out of my academic laboratories. The company has raised over £30M and developed the first commercially available autoantibody test for the early detection of lung cancer (EarlyCDT-Lung). With the support of the University of Nottingham I have been responsible for the scientific and technical developmental work of Oncimmune.

In addition to EarlyCDT-Lung being commercially available the company has just committed to two prospective tests which will specifically assess the health economic benefit of EarlyCDT-Lung.

EarlyCDT is a platform technology which is applicable to all solid tumours. The company is now focused on developing a test for hepatocellular cancer (www.oncimmune.com).

ii) FaHRAS

FaHRAS developed software to help physicians assess breast cancer risk (using different breast cancer risk models) and links with the UK NICE guidelines. The software has been extensively tested is now used in secondary and tertiary NHS units in the UK and Ireland, Australia and the Caribbean. A version for primary care has been developed and is about to be launched. We are also developing lung and colon cancer risk models.

iii) Specimen collection company

I was one of four individuals who established a specimen collection company which could collect samples from patients with most types of tumours and also appropriate controls. I resigned from the company soon after starting it because of potential conflicts of interest with a second of the spinout companies. This company continues to develop 10 years after I helped start it.

BREAST CANCER ON-LINE

I am Editor-in-Chief of the web journal, Breast Cancer On-Line (BCO). This website (www.bco.org) was the first dedicated solely for professionals working in the field of breast cancer. The membership is over 25,000.

GUIDELINES

i) BASO GUIDELINES FOR MANAGEMENT OF BONE METASTASES IN BREAST CANCER

I was a member of a working party which has produced the first edition of the BASO Guidelines for Management of Bone Metastases in Breast Cancer. These guidelines follow the highly respected work by BASO in producing guidelines both for surgeons in breast cancer screening and for symptomatic breast disease.

ii) GUIDELINES FOR SCREEN-DETECTED AND SYMPTOMATIC BREAST CANCER

I was an invited, expert reviewer for the latest National Breast Guidelines which were issued in 2009.

TRAVELLING FELLOWSHIPS

Moynihan Travelling Fellowship from Association of Surgeons of Great Britain and Ireland, 1993

Wellington Foundation. 1993

Dr Robert Malcolm Trust, l993

Royal College of Physicians and Surgeons of Glasgow, 1993

I had the opportunity in 1993 as the Moynihan Travelling Fellow to visit six of the large comprehensive cancer centres in the USA (Boston, Washington, Duke University at Durham, San Francisco, San Antonio and New York). At each centre I focused my visit on the breast cancer programme. This further widened my clinical experience as well as my personal contacts with clinical, and basic, scientists in the USA. These initial contacts have developed over the past twenty years and have resulted in a variety of valuable collaborations.

MEMBERSHIP OF LEARNED SOCIETIES

Society of Academic and Research Surgery

British Association of Surgical Oncology

Association of Breast Surgery

British Association of Cancer Research

British Breast Group

Association of Surgeons of Great Britain and Ireland

American Society of Clinical Oncology

MEMBERSHIP OF COMMITTEES (Past and Current)

University

Member of Faculty Board

Member of Admissions Committee (Faculty of Medicine and Health Sciences)

University representative on Post-graduate Education Centre Council

Masters Steering Committee

Medicine and Surgery Working Party for the undergraduate curriculum

Health Authority

Mid Trent Higher Surgical Training Committee

Nottingham City Hospital

Trustee of the Medical Research Centre

Member of Breast Services Directorate

Medical Records Committee
Counselling and Communication Skills Steering Group

Hospital Medical Committee

Nottingham Cancer Centre

Education and Training Committee (Chairman)

Scientific

British Association of Surgical Oncology (BASO)
(National Committee)

BASO Education and Training Committee (member)

UKCCCR Tumour Marker Sub-Committee (member)

European Study Group for Blood Tumour Markers in Breast Cancer
(Chairman of Administrative Board)

Nottingham International Breast Cancer Meeting

(Scientific and Organising Committee)

Breast Cancer On-line
Editor-in-Chief

BASO Working Party for Guidelines on Management of Bone Metastases in Breast Cancer (member)

European Healthcare Innovation Leadership Network - Breast Cancer Working Group 2009 (member)

STEERING COMMITTEES, DATA and SAFETY MONITORING COMMITTEES

Steering Committees

FH01
FH02
Neo-excel
EPHOS
POETIC

DSMC

SOFEA
TNT

INTERESTS AND OTHER ACTIVITIES

B.SC. IN PARASITOLOGY

During 1976-77 I took time out of my medical course to complete an intercalated B.Sc. in Parasitology at the University of Glasgow. This was carried out under the Zoology Department and included lectures, seminars and laboratory work in Protozoology, Parasitology and Medical Entomology. During this period I also successfully completed a degree course in Biophysics.

CAMBRIDGE DIPLOMA IN RELIGIOUS STUDIES

During 1981-82, following my year as a house officer in general surgery and medicine, I took one year out of my post-graduate medical education. During this year I was in full-time study funded by myself. This was a two-year course which I completed in one year. At the end of that year I successfully presented myself for the Cambridge Diploma in Religious Studies. One of six papers was a medical ethics thesis.

CLUBS AND SOCIETIES

i) Arderne Surgical Society (Secretary) - Nottingham Surgical Society

ii) Nottingham University Club

PUBLICATIONS - Papers in refereed journals

1985

1) Local anaesthesia of the great toe
Robertson JFR, Muckart DJJ. J Royal Coll. Surg. Edinburgh 1985; 30: 237-8

1986

2) Intravenous nutrition and hepatic dysfunction
Robertson JFR, Garden OJ, Shenkin A. J Parent Enter Nutr. 1986; 10: 17 -6

3) Simultaneous intussusception and volvulus due to a congenital band
Roberson JFR, Howatson A. Scot Med J. 1986; 31: 245-6

4) Local excision of ampullary carcinoma
Robertson JFR, Imrie CW. Acta Chir Scand. 1986; 152: 537-9

1987

5) Facial paralysis due to acute parotitis
Robertson JFR, Azmy AF. Kinderchirurgie. 1987; 42: 312

6) Circumcaval ureter: treatment of an asymptomatic child
Robertson JFR, Azmy AF. Akt Urol. 1987; 18: 1555 – 1565

7) Surgery in necrotising enterocolitis
Robertson JFR, Azmy AF, Young DG. Br J Surg. 1987; 74: 387-9

8) Intradiaphragmatic abscess
Ballantyne KC, Robertson JFR. Br JHM. 1987; 38: 369

9) Acute pancreatitis associated with carcinoma of the ampulla of Vater
Robertson JFR, Imrie CW. Br J Surg. 1987; 74: 395-7

10) Management of periampullary carcinoma
Robertson JFR, Imrie CW, Hole DJ, Carter DC, Blumgart H. Br J Surg. 1987; 74: 816-9

1988

11) The effect of LHRH agonist, Zoladex, on ovarian histology
Williamson K, Robertson JFR, Ellis IO, Nicholson RI, Elston CW, Blamey RW. Br J Surg. 1988; 75: 595-6

12) Comparison of mastectomy with tamoxifen for treating elderly patients with operable breast cancer
Robertson JFR, Todd JH, Ellis IO, Elston CW, Blamey RW. BMJ. 1988; 297: 511–4

13) Immunocytochemical localisation of oestrogen receptors in human breast tissue
Walker KJ, Bouzubar N, Robertson JFR, Ellis IO, Elston CW, Blamey RW, Wilson DW, Griffiths K, Nicholson RI. Cancer Res. 1988; 48: 6517-22

14) Cholelithiasis in children - a follow-up study
Robertson JFR, Carachi R, Sweet EM, Raine PAM. J Paed Surg. 1988; 23: 246-9

15) Assent to ascent of the testis
Robertson JFR, Azmy AF, Cochrane W. Br J Urol. 1988; 61: 146-7

16) Bladder calculus: a complication of the Gel Vernet technique of ureteric re-implantation
Robertson JFR, Azmy AF. Br J Urol. 1988; 61: 95

17) Choledochal cysts in children and adults - a 30 year review of Glasgow Teaching Hospitals
Robertson JFR, Raine PAM. Br J Surg. 1988; 75: 799-801

18) Appropriate technology spring retractor
Richardson JB, Robertson JFR. Tropical Doctor. 1988; 18: 143 – 144

19) Patients with ampullary carcinoma are prone to other malignant tumours
Robertson JFR, Boyle P, Imrie CW. Br J Cancer. 1988; 58: 216-8

1989

20) Scrotal carcinoma following prolonged use of crude coal tar ointment
McGarry G, Robertson JFR. Br J Urol. 1989; 63: 211

21) Factors predicting the response of patients with advanced breast cancer to endocrine (Megace) therapy
Robertson JFR, Williams MR, Todd JH, Nicholson RI, Morgan DAL, Blamey RW. Eur J Cancer Clin Oncol. 1989; 25: 469-75

22) Endocrine effects of combination antioestrogen and LH-RH agonist therapy in premenopausal advanced breast cancer patients
Walker KJ, Turkes A, Robertson JFR, Blamey RW, Griffiths K, Nicholson RI. Eur J Cancer Clin Oncol. 1989; 25: 651-4

23) Combined endocrine effects of LHRH agonist (Zoladex) and Tamoxifen (Nolvadex) in pre-menopausal women with breast cancer
Robertson JFR, Walker K, Nicholson RI, Blamey RW. Br J Surg. 1989; 76: 1262-5

24) Mitoxantrone - a useful palliative therapy in advanced breast cancer
Robertson JFR, Williams MR, Todd JH, Blamey RW. Am J Clin Oncol. 1989; 12: 393-6

25) Granulomatous lobular mastitis
Galea M, Robertson JFR, Ellis IO, Elston CW, Blamey RW. ANZ J Surg. 1989; 59: 547-50

26) Ki 67 immunostaining in primary breast cancer: pathological and clinical associations
Bouzubar N, Walker K, Nicholson RI, Ellis IO, Elston CW, Robertson JFR, Blamey RW. Br J Cancer. 1989; 59: 943-7

27) Carcinoembryonic antigen immunocytochemistry of primary breast cancer
Robertson JFR, Ellis IO, Bell J, Todd JH, Robins A, Elston CW, Blamey RW. Cancer. 1989; 64: 1638-45

28) An observation of DNA ploidy, histological grade, and immunoreactivity for tumour-related antigens in primary and metastatic breast carcinoma
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Invited Publications and Book Chapters

1) Oestrogen deprivation in breast cancer using LH-RH agonists and antioestrogens
Nicholson, R.I., Walker, K.J., Walker, R.F., Read, C.F., Finley, E., Robertson, J.F.R., Blamey, R.W., Griffiths, K.
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2) Distribution and prognostic significance of oestrogen receptor negative cells in oestrogen receptor positive breast tumours
Walker, K.J., Bouzabar, N., Elston, C.W., Ellis, I.O., Robertson J.F.R., Blamey, R.W., Griffiths, K.
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3) GnRH analogues in breast cancer
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4) McKenna, P.G., O'Neill, K.L., Abram, W.P., Robertson, J.F.R., Blamey R.W.
In: Thymidine Kinase - A marker for neoplastic and viral diseases (Oehr, P.; Ed)
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5) Review of the endocrine actions of LH-RH analogues in premenopausal women with breast cancer
Nicholson, R.I, Walker, K.J, Walker, R.F, Read, G.F, Turkes, A, Robertson, J.F.R, Blamey, R.W.
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6) Zoladex in advanced breast cancer
Robertson, J.F.R., Nicholson, R.I., Walker, K.J. and Blamey, R.W.
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7) The management of breast cancer
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9) The role of serum markers in breast cancer.
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14) erbB signalling and endocrine sensitivity of human breast cancer. In: EGF receptor in tumour growth and progression.
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16) Prognostic and response markers in the management of breast cancer.
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EXHIBIT B: MATERIALS CONSIDERED LIST

Exhibit	Description
2004	Angelo Di Leo et al., *Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg With Fulvestrant 500 mg in Postmenopausal Women With Estrogen Receptor-Positive Advanced Breast Cancer*, 28 J. Clin. Oncol. 4594 (2010) ("Di Leo 2010")
2005	Angelo Di Leo et al., *Final Overall Survival: Fulvestrant 500 mg vs 250 mg in the Randomized CONFIRM Trial*, 106 J. Nat'l Cancer Inst. 1 (2014) ("Di Leo 2014")
2006	S. Ohno et al., *Three dose regimens of fulvestrant in postmenopausal Japanese women with advanced breast cancer: results from a double-blind, phase II comparative study*, 21 Annals Oncol. 2342 (2010) ("FINDER I")
2007	Kathleen I. Pritchard et al., *Results of a phase II study comparing three dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer (FINDER2)*, 123 Breast Cancer Res. & Treat. 453 (2010) ("FINDER II")
2008	Robert T. Greenlee et al., *Cancer Statistics, 2000*, 50 CA Cancer J. Clin. 7 (2000) ("Greenlee")
2009	J.F.R. Robertson, *Oestrogen receptor: a stable phenotype in breast cancer*, 73 Brit. J. Cancer 5 (1996) ("Robertson 1996")
2010	Monica Fornier et al., *Update on the Management of Advanced Breast Cancer,* 13 Oncology 647 (1999) ("Fornier")
2011	V. Craig Jordan, *Alternate Antiestrogens and Approaches to the Prevention of Breast Cancer*, 22 J. Cell. Biochem. 51 (Supp. 1995) ("Jordan Supp. 1995")
2012	Gabriel N. Hortobagyi et al., *Anastrozole (Arimidex®), a New Aromatase Inhibitor for Advanced Breast Cancer: Mechanism of Action and Role in Management*, 16 Cancer Investigation 385 (1998) ("Hortobagyi Cancer Investigation 1998")
2013	S.R.D. Johnston et al., *The novel anti-oestrogen idoxifene inhibits the growth of human MCF-7 breast cancer xenografts and reduces the frequency of acquired anti-oestrogen resistance*, 75 Brit. J. Cancer 804 (1997) ("Johnston 1997")
2014	Kathleen Pritchard, *Effects on Breast Cancer: Clinical Aspects*, *in* Estrogens and Antiestrogens: Basic and Clinical Aspects 175 (R. Lindsay et al. eds., 1997) ("Pritchard 1997")

EXHIBIT B: MATERIALS CONSIDERED LIST

Exhibit	Description
2015	Aman U. Buzdar et al., *Tamoxifen and Toremifene in Breast Cancer: Comparison of Safety and Efficacy,* 16 J. Clin. Oncol. 348 (1998) ("Buzdar Clin. Oncol. 1998")
2016	Aman U. Buzdar et al., *Update on Endocrine Therapy for Breast Cancer*, 4 Clin. Cancer Res. 527 (1998) ("Buzdar Clin. Cancer Res. 1998")
2017	V. Craig Jordan, *TAMOXIFEN: Toxicities and Drug Resistance During the Treatment and Prevention of Breast Cancer*, 35 Ann. Rev. Pharmacol. Toxicol. 195 (1995) ("Jordan 1995")
2018	Monica Morrow et al., *Molecular Mechanisms of Resistance to Tamoxifen Therapy in Breast Cancer*, 128 Arch. Surg. 1187 (1993) ("Morrow")
2019	Valerie J. Wiebe et al., *Tamoxifen resistance in breast cancer*, 14 Crit. Revs. Oncol. Hematol. 173 (1993) ("Wiebe")
2020	V. Craig Jordan, *The Strategic Use of Antiestrogens to Control the Development and Growth of Breast Cancer*, 70 Cancer 977 (Supp. 1992) ("Jordan Supp. 1992")
2021	V. Craig Jordan, *The Role of Tamoxifen in the Treatment and Prevention of Breast Cancer*, Curr. Probl. Cancer 134 (1992) ("Jordan 1992")
2022	Susan E. Minton, *New Hormonal Therapies for Breast Cancer*, 6 Cancer Control J. 1 (1999) ("Minton")
2023	T.A. Grese et al., *Selective Estrogen Receptor Modulators (SERMs)*, 4 Current Pharm. Design 71 (1998) ("Grese 1998")
2024	Gabriel N. Hortobagyi, *Treatment of Breast Cancer*, 339 New Eng. J. Med. 974 (1998) ("Hortobagyi New Eng. J. Med. 1998")
2025	Shigeru Masamura et al., *Aromatase inhibitor development for treatment of breast cancer*, 33 Breast Cancer Res. & Treat. 19 (1994) ("Masamura 1994")
2026	Gary J. Kelloff et al., *Aromatase Inhibitors as Potential Cancer Chemopreventives*, 7 Cancer Epidemiol., Biomarkers & Prevention 65 (1998) ("Kelloff 1998")
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EXHIBIT B: MATERIALS CONSIDERED LIST

Exhibit	Description
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2042	AACR Journals Online
2125	Affidavit of Internet Archive (Oct. 2016) ("Affidavit of Internet Archive")
2043	Declaration of Sandra McLeskey, Ph.D. (Oct. 1, 2014) ("McLeskey Declaration")
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2045	Physician's Desk Reference, 53rd ed., 3425-28 (1999) ("PDR 1999 Nolvadex®")
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2047	R.J. Santen, *Use of aromatase inhibitors in breast carcinoma*, 6 Endocrine-Related Cancer 75 (1999) ("Santen")
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2063	Stephen R.D. Johnston et al., *Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroisal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicenter, phase 3 randomised trial*, 14 Lancet Oncol. 989 (2013) ("Johnston 2013")
2064	J.F.R. Robertson et al., *Sensitivity to further endocrine therapy is retained following progression on first-line fulvestrant*, 92 Breast Cancer Res. & Treat. 169 (2005) ("Robertson 2005")
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2075	I. Vergote et al., *Fulvestrant, a new treatment option for advanced breast cancer: tolerability versus existing agents*, 17 Ann. Oncol. 200 (2006) ("Vergote 2006")
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