Scharff v. Wyeth, et al Doc. 238

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

HAROLD H. SCHARFF, administrator of the estate of Kathleen Scharff,	)	
Plaintiff,	)	
v.	)	CASE NO. 2:10-CV-220-WKW [WO]
WYETH, *et al.*,	)	
Defendants.	)	

MEMORANDUM OPINION AND ORDER

On August 2, 2011, the court entered a Memorandum Opinion and Order (Doc. # 223 (the "Order")) partially granting Defendants' (collectively "Wyeth") motion for summary judgment.[1] In the Order, the court instructed Plaintiff Kathleen Scharff,[2] pursuant to Rule 56(f) of the Federal Rules of Civil Procedure, to show cause "why summary judgment should not be granted on her remaining wanton failure to warn

[1] In the Order, the court granted summary judgment for Wyeth on Mrs. Scharff's negligence, AEMLD, breach of express warranty, fraud, and civil conspiracy claims. (Order 18, 48.) The ruling was based upon grounds other than a lack of causation, and ruling was reserved on Wyeth's causation arguments. (Order 48.)

[2] Harold H. Scharff has since been substituted as Plaintiff. (Doc. # 232.) The remaining claims are referred to as belonging to Mr. Scharff as administrator of Mrs. Scharff's estate. (Doc. # 232.)

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and wanton design claims."[3] (Order 49 (citing relevant cases).) Mr. Scharff timely responded with a brief and 173 accompanying exhibits. (Doc. # 227 (the "Response").) Wyeth timely replied with a brief and 59 accompanying exhibits. (Doc. # 231 (the "Reply").) After careful consideration of the arguments of counsel, the applicable law and the voluminous record, summary judgment is due to be granted in favor of Wyeth on Mr. Scharff's remaining wantonness claims.

I. FACTS[4]

The facts pertinent to this opinion are detailed below. The facts in Parts A through C are incorporated from the court's earlier factual findings in the Order.[5] (Order 6-15.) Part D details the pertinent facts surrounding Wyeth's alleged wantonness.

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[3] Mrs. Scharff was given notice and a reasonable time to respond to the show cause order. Fed. R. Civ. P. 56(f); *Massey v. Congress Life Ins. Co.*, 116 F.3d 1414, 1417 (11th Cir. 1997) (District court must give ten days notice for the plaintiff to respond in opposition to *sua sponte* summary judgment.).

[4] The actual facts may be different than those stated here. *See Lee v. Ferraro*, 284 F.3d 1188, 1190 (11th Cir. 2002) ("[F]acts, as accepted at the summary judgment stage of the proceedings, may not be the actual facts of the case. Nevertheless, for summary judgment purposes, [the] analysis must begin with a description of the facts in the light most favorable to the plaintiff." (citation and internal quotation marks omitted)).

In the interest of brevity, discussion of jurisdiction, venue and the standard of review is omitted because the former is undisputed and the latter is well settled. (Order 2-5.)

[5] The evidentiary references in the Order are unchanged here. Though Mr. Scharff has highlighted additional evidence in the "Brief Factual Background" section of the Response (Response 13-18), that evidence is not necessary to the wantonness determination at issue in this opinion.

A. Mrs. Scharff Is Prescribed Prempro

On August 28, 1997, when she was fifty-five years old and a resident of Boaz, Alabama, Mrs. Scharff was prescribed Prempro by her primary physician, Dr. Andrew Reiland. (Doc. # 76, Ex. B, at 27 ("Scharff Dep. Vol. I"); Doc. # 88, Ex. A; Doc. # 88, Ex. B, at 4, 52 ("MDL Fact Sheet").) Dr. Reiland prescribed Prempro for Mrs. Scharff because of her menopausal symptoms, including extreme hot flashes and extreme vaginal dryness. (Doc. # 76, Ex. C, at 121-22 ("Dr. Reiland Dep."); Doc. # 76, Ex. A, at 17-18 ("Scharff Dep. Vol. II"); Doc. # 88, Ex. A.) Dr. Reiland did not prescribe Prempro to Mrs. Scharff to prevent osteoporosis or Alzheimer's disease, or for heart protection, nor did he tell her of such benefits. (Scharff Dep. Vol. II, at 21-23.) At the time of her prescription, Mrs. Scharff did not recall receiving a book, brochure, or other information about menopause from Dr. Reiland. (Scharff Dep. Vol. II, at 21.) Mrs. Scharff relied solely on Dr. Reiland's advice in deciding to take Prempro, and she did not recall seeing any advertisements for Prempro before or during the period she took Prempro. (Scharff Dep. Vol. I, at 81; Scharff Dep. Vol II, at 19, 78.) Mrs. Scharff recalled that her Prempro prescription package probably included the Patient Information Insert, that she probably glanced at it, but that she did not read it. (Scharff Dep. Vol. I, at 77, 138-39; Scharff Dep. Vol. II, at 26.)

1. Background on Prempro

Prempro comes in pill form and combines Premarin, conjugated estrogens, and Medroxyprogesterone acetate, a synthetic progestin. (Doc. # 88, Ex. C, at 3120 (1998 Physicians' Desk Reference ("1998 PDR")).) At the time of Mrs. Scharff's prescription, Prempro was manufactured by Ayerst Laboratories, Inc., which was then owned by Wyeth-Ayerst, a predecessor in interest to Wyeth, LLC. (Doc. # 88, at 7; 1998 PDR, at 3124.) In 1994, the Food and Drug Administration ("FDA") approved Prempro for the treatment of menopausal symptoms and for the prevention of osteoporosis. (Doc. # 76, Ex. E ("1994 FDA Approval").) The language of Prempro's 1998 Patient Information Insert is found in the 1998 PDR, which the parties agree contains substantially the same language as the 1997 PDR and Patient Information Insert. (Doc. # 88, at 8 & n.3; Doc. # 77, at 4 n.1.) Prempro's Patient Information Insert, as reproduced in the 1998 PDR, included the following warning:

> **WARNINGS**
> ALL WARNINGS BELOW PERTAIN TO THE USE OF THIS COMBINATION PRODUCT.
> Based on experience with estrogens and/or progestins:
> 1. *Induction of malignant neoplasms Breast Cancer.* Some studies have reported a moderately increased risk of breast cancer (relative risk of 1.3 to 2.0) in those women on estrogen replacement therapy taking higher doses or in those taking lower doses for prolonged periods of time, especially in excess of 10 years. The majority of studies, however, have not shown an association in women who have ever used estrogen replacement therapy. The effect of added progestins on the risk of breast cancer is unknown, although a

moderately increased risk in those taking combination estrogen/progestin therapy has been reported. Other studies have not shown this relationship. In a one year clinical trial of PREMPRO, PREMPHASE®, and Premarin alone, 5 new cases of breast cancer were detected among 1377 women who received the combination treatments, while no new cases were detected among 347 women who received Premarin alone. The overall incidence of breast cancer in this clinical trial does not exceed that expected in the general population. In the three year clinical Postmenopausal Estrogen Progestin Intervention (PEPI) trial of 875 women to assess differences among placebo, unopposed Premarin, and three different combination hormone therapy regimens, one (1) new case of breast cancer was detected in the placebo group (n=174), one [(1)] in the Premarin alone group (n=175), none in the continuous Premarin plus continuous medroxyprogesterone acetate group (n=174), and two (2) in the continuous Premarin plus cyclic medroxyprogesterone acetate group (n=174). Women on hormone replacement therapy should have regular breast examinations and should be instructed in breast self-examination, and women over the age of 50 should have regular mammograms.

(1998 PDR at 3121-22; Doc. # 88, at 7-8.) It also warned that:

RISKS OF ESTROGENS AND/OR PROGESTINS

. . .

Cancer of the Breast. Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used high doses for shorter time periods. The effects of added progestin on the risk of breast cancer are unknown. Some studies have reported a somewhat increased risk, even higher than the possible risk associated with estrogens alone. Others have not. Regular breast examinations by a health professional and monthly self-examination are recommended for all women. Regular mammograms are recommended for all women over 50 years of age.

(1998 PDR at 3124; Doc. # 88, at 8.)

2. Dr. Reiland's Knowledge Concerning Prempro

In 1997, when Dr. Reiland prescribed Prempro to Mrs. Scharff, he had background knowledge of the risk of breast cancer associated with hormone replacement therapy. (Dr. Reiland Dep. 39.) Dr. Reiland would discuss this breast cancer risk with his patients when prescribing hormone replacement therapy, but he "would always say that the majority of the studies seemed to be reassuring." (Dr. Reiland Dep. 108-09.) Dr. Reiland recognized in 1997 that there was conflicting literature regarding the association of breast cancer and hormone replacement therapies. (Dr. Reiland Dep. 39-40.) He also indicated that he was a little skeptical of the 1997/1998 PDR language stating that "the majority of studies have not shown an association [with a higher risk of breast cancer] in women who have ever used [estrogen replacement therapy]," because some of those studies may have been inaccurate. (Dr. Reiland Dep. 39.)

Dr. Reiland also testified that the 1998 PDR label referencing the Postmenopausal Estrogen Progestin Intervention ("PEPI") trial did not indicate a greater chance of breast cancer associated with hormone replacement therapy relative to the background population, and that he found this to be "somewhat reassuring." (Dr. Reiland Dep. 40-41, 43-44.) When asked about Prempro's 2007 PDR label, Dr. Reiland found its black box label to be comparably stronger than the 1997-99 PDR

labels for Prempro. (Dr. Reiland Dep. 47-50.) He also stated that he wished that he had had that information available in 1997, and that he would have passed that information along to Mrs. Scharff. (Dr. Reiland Dep. 47-50.) He also believed that if Wyeth's sales representatives had the 2007 label information in 1997 or 1998, they would have passed it along to him. (Dr. Reiland Dep. 50-51.) Dr. Reiland agreed that accurate information about a drug was important to a doctor's risk/benefit analysis. (Dr. Reiland Dep. 63-65.) If a drug's risks outweighed its benefits, Dr. Reiland said that he generally would not have prescribed it, but ultimately the decision to take a drug would be up to the patient and he would pass along all the available information to the patient. (Dr. Reiland Dep. 65-66.)

Dr. Reiland's decision to prescribe Prempro to Mrs. Scharff was not affected by any Wyeth sales representatives' calls or promotional materials, though he did receive sales calls from Wyeth sales representatives before, during, and after his prescription of Prempro to Mrs. Scharff. (Dr. Reiland Dep, 21-22, 142; Doc. # 88, Ex. J.) According to Wyeth's sales records, Dr. Reiland met with Susan Hendrick, a Wyeth sales representative, on July 1, 1997. She reported in her notes, "[Dr. Reiland] has used the Premphase and said that we need to have more info on it to give to the patient[;] I gave him the tear-off sheets and left videos and pamphlets for his patients. We really do need more give-aways for Premphase for these docs that

areusing [sic] it." (Doc. # 88, Ex. J.) On November 25, 1997, she reported that "[Dr. Reiland] said that he loves the XXXXXXX and hasn't heard back from any girls he has put it on[.] Liked the XXX and said that it was about time that we made it once a day - much easier[.] Premarin and lowering lipids - he heartily agreed[.]" (Doc. # 88, Ex. J.)

B. Mrs. Scharff's Breast Cancer Diagnosis and Treatment

Ms. Scharff took Prempro as prescribed from August 28, 1997, to January 26, 1999. (MDL Fact Sheet at 4; Scharff Dep. Vol. II, at 24.) Prempro was the only hormone replacement drug that Mrs. Scharff ever took, and Dr. Reiland was the only doctor who prescribed it for her. (Scharff Dep. Vol. II, at 72.) Prempro alleviated Mrs. Scharff's menopausal symptoms, but those symptoms returned once she stopped taking the drug. (Scharff Dep. Vol. II, at 72-73.) On September 24, 1998, approximately thirteen months after she began taking Prempro, Mrs. Scharff visited Dr. Reiland and reported that she felt a lump in one of her breasts. (Dr. Reiland Dep. 130; Scharff Dep. Vol. I, at 39.) Dr. Reiland immediately referred Mrs. Scharff to Dr. Naughton, a local surgeon, for a follow-up on the lump in her breast. (Scharff Dep. Vol. I, at 39.) On September 25, 1998, she received a mammogram from Dr. Reiland, and Mrs. Scharff visited Dr. Naughton. (Dr. Reiland Dep. 131; Scharff Dep. Vol. I, at 39, 42.) According to Mrs. Scharff, Dr. Naughton told her, "Let's just watch it.

It's probably nothing." (Scharff Dep. Vol. II, at 32.) Dr. Naughton recalled that he recommended a short follow-up and a re-evaluation. (Doc. # 88, Ex. L, at 14 ("Dr. Naughton Dep.").)

In early January 1999, Dr. Naughton called Mrs. Scharff and told her, "We have to have that checked." (Scharff Dep. Vol. II, at 32-33.) On January 12, 1999, Mrs. Scharff visited Dr. Naughton, who performed a biopsy on the lump in her breast and sent the biopsy off for analysis. (Dr. Reiland Dep. 132; Scharff Dep. Vol. II, at 32-33; Doc. # 76, Ex. H ("Dr. Naughton January 13, 1999 Record").) On January 13, 1999, the Gadsden Regional Medical Center Pathology Department issued a pathology report diagnosing her breast tissue biopsy as: "BREAST, RIGHT, SURGICAL BIOPSY: INVASIVE MODERATELY DIFFERENTIATED DUCTAL CARCINOMA . . . ."[6] (Dr. Naughton January 13, 1999 Record.) Plaintiff's evidence is that Mrs. Scharff was told of her breast cancer diagnosis on January 18, 1999, by Dr. Naughton. (Doc. # 88, at 19; Doc. # 88, Ex. M.) At that same time, Dr. Naughton

[6] Whether Mrs. Scharff's breast cancer was ductal or tubular-lobular is hotly contested. The initial report of ductal cancer is referenced here as it pertains to the date her breast cancer was diagnosed, but the court does not draw the factual conclusion that her breast cancer was ductal. Such a factual conclusion is unnecessary to this memorandum opinion.

also told her to stop taking Prempro, and she did.[7] (Scharff Dep. Vol. I, at 71.) Mrs. Scharff did not ask Dr. Naughton why he was instructing her to stop taking Prempro, nor did Dr. Naughton recall Mrs. Scharff asking him if hormone therapy caused her breast cancer. (Scharff Dep. Vol. II, at 80, 86-87; Dr. Naughton Dep. 32-33.) There is also no evidence in the record that she asked Dr. Reiland about the cause of her breast cancer.

After consulting with a radiation oncologist, Mrs. Scharff elected to have a radical mastectomy done on her right breast. (Dr. Naughton Dep. 31-32; Scharff Dep. Vol. II, at 34.) Mrs. Scharff's mastectomy of her right breast was performed by Dr. Naughton on January 26, 1999.[8] (Dr. Reiland Dep. 134; Dr. Naughton Dep. 36-38.) On February 2, 1999, Mrs. Scharff's breast cancer was diagnosed as both ER+ (estrogen receptor positive) and PR+ (progestin receptor positive). (Doc. # 88, Ex. O ("February 2, 1999 Lab Report").)

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[7] The MDL fact sheet reflects that Mrs. Scharff ceased taking Prempro on January 26, 1999, over a week after she was told of her cancer diagnosis. (MDL Fact Sheet 4.) However, the MDL fact sheet also reflects that "[Dr. Naughton] instructed plaintiff to discontinue hormone therapy" on January 11, 1999. (MDL fact Sheet 54.) These factual inconsistencies are immaterial here.

[8] Mrs. Scharff later elected to have a mastectomy performed on her left breast due to shoulder pain and general discomfort, and to avoid continued consumption of the drug tamoxifen. (Scharff Dep. Vol. I, at 61-62; Scharff Dep. Vol. II, at 35-36, 79-80.)

C. The Women's Health Initiative, Prempro, and Mrs. Scharff

The National Institutes of Health published its report of the Women's Health Initiative ("WHI") on July 9, 2002. (Doc. # 88, Ex. P ("WHI Press Release").) A brief description of the WHI study follows:

> The estrogen plus progestin trial of the WHI involved 16,608 women ages 50 to 79 years with an intact uterus. An important objective of the trial was to examine the effect of estrogen plus progestin on the prevention of heart disease and hip fractures, and any associated change in risk for breast and colon cancer. The study did not address the short-term risks and benefits of hormones for the treatment of menopausal symptoms.

(WHI Press Release 2.) The WHI Press Release also stated that "[t]he National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) [ ] stopped early a major clinical trial of the risks and benefits of combined estrogen and progestin in healthy menopausal women due to an increased risk of invasive breast cancer." (WHI Press Release 1.) The study was stopped after an average follow-up period of 5.2 years. (WHI Press Release 1.) The WHI Press Release explained that the estrogen plus progestin group in the study experienced a 26 percent increase in breast cancer compared to the placebo group. (WHI Press Release 4.)

The publication of the WHI study in July 2002 garnered a great deal of media attention. (*See, e.g.*, Dr. Reiland Dep. 68.) Dr. Reiland testified that the study found that there was an increased incidence of breast cancer in the study population, which

had a profound impact on his understanding of the risks and benefits involved in hormone replacement therapy. (Dr. Reiland Dep. 68-69.) It was not, however, the first time he had been made aware of the increased incidence of breast cancer associated with hormone replacement therapy. (Dr. Reiland Dep. 71.) He noted a change in the labeling of Prempro after the WHI study was published. (Dr. Reiland Dep. 72-73.)

Mrs. Scharff did not recall the publication of the WHI study or reading anything about the findings of that study. (Scharff Dep. Vol. II, at 39-40.) However, Mrs. Scharff did begin to connect her breast cancer to her consumption of Prempro sometime between 2003 and 2005 when she "started seeing more articles in the paper and stuff like that." (Scharff Dep. Vol. II, at 39, 78.) During that period, she collected newspaper clippings of articles discussing the association of hormone replacement therapy and breast cancer. (Scharff Dep. Vol. II, at 39-40.)

D. Wyeth's Allegedly Wanton Conduct

The following evidence, relevant to the remaining wantonness claims, was produced by Mr. Scharff and Wyeth in response to the court's show cause order.[9]

In his Response, Mr. Scharff argues that Wyeth's wanton conduct occurred along three lines of operation. (Response 26.) First, Wyeth knew that safety studies

[9] Evidence from Wyeth is only cited where it is undisputed by Mr. Scharff's evidence.

on estrogen and progestin hormone therapy ("E+P") were needed, but deliberately refused to conduct those studies. (Response 26.) Second, Wyeth failed to tell doctors the truth about the breast cancer risk of E+P based upon the then-existing science, and took affirmative steps to stop doctors and women from learning the actual risks and benefits of E+P. (Response 26.) Third, Wyeth promoted its hormone drugs for untested, unproven and off-label heart and mental benefits. (Response 26.) In light of the limited scope of the Order and the wantonness claims at issue, the court now turns to the relevant facts.

1. Wyeth's Knowledge of the Need for Additional Studies Concerning the Risk of Breast Cancer Associated with Combination Estrogen and Progestin Hormone Replacement Therapy

Mr. Scharff opens his discussion of the facts surrounding Wyeth's knowledge of the risk of Prempro with a lengthy discussion of estrogen replacement therapy ("ERT") and its effect on endometrial cancer in the 1970s. (Response 27-30.) Mr. Scharff then turns to Wyeth's promotion of the combination use of Premarin and a progestin "off-label" in the 1980s to treat menopausal symptoms. (Response 30-31.) During this period, long before Mrs. Scharff was prescribed Prempro in 1997 or Prempro was approved by the FDA in 1994, Wyeth did not conduct any E+P breast cancer studies. (Response 31.) Following is a chronological summary of evidence of

Wyeth's knowledge concerning the need for additional studies of the breast cancer associated with E+P.[10]

In a 1977 study concerning the use of estrogen for osteoporosis, the Endocrinology and Metabolism Advisory Committee of the FDA noted that "[t]here is insubstantial evidence that there may be additional risk of increased breast cancer but this is at this time unsubstantiated." (Response, Ex. 43, at 1.) A 1983 Wyeth memorandum stated that "[t]here is not adequate evidence in the literature for any estrogen / progesterone regimen which would meet FDA standards."[11] (Response, Ex. 44.) At a 1983 "Estrogens Workshop" sponsored by the NHLBI-NIH, Wyeth representative Dr. John Mullane reported his overall impression that "the participants in the workshop were favorably disposed to the conduct of a relatively large, long-term, NIH-type study on the effects of estrogens on morbidity and mortality." (Response, Ex. 45.) In a 1983 internal memorandum, Wyeth representative Arnold Somin wrote a memorandum concerning the "Desired Labeling and Indications" of a product called Prem-Pak. (Response, Ex. 47.) Prem-Pak was an E+P combination

[10] Combined estrogen and progestin hormone therapy is referred to as E+P. Some of the studies refer to E+P as HRT, while others fold both estrogen replacement therapy ("ERT") and E+P under the umbrella of HRT. The court has attempted to be as consistent as possible by using "E+P" for combination hormone therapy and "estrogen" or "ERT" for non-combination hormone therapy.

[11] Wyeth's various successors-in-interest are referred to as Wyeth throughout the opinion.

therapy consisting of a single package of Premarin and "a progestin for cyclic use." (Response, Ex. 47.) Regarding Prem-Pak, Mr. Somin expressed his concern with the FDA and the consequences "that could arise if the FDA were to take the position that PREM-PAK is equivalent to a combination drug product of the type requiring demonstration that the combination does more than its components in regard to each indication for the combination product. To attempt such demonstration would be very costly, would take many years, and might in the end not prove successful." (Response, Ex. 47.) In fact, he admitted that "the results of the studies that would be needed could turn out to be embarrassing. To avoid this issue, [Wyeth] ha[s] taken the position that the progestin is used to prevent or minimize a potential adverse effect of PREMARIN (endometrial hyperplasia) and, thereby, to enhance the safety of PREMARIN." (Response, Ex. 47.)

In 1985, the FDA denied Wyeth's Prem-Phase New Drug Application. (Response, Ex. 46.) Wyeth representative John R. Rapoza represented that it was then the FDA's opinion "that clinical trials with Prem-Phase will be necessary prior to approval." (Response, Ex. 46.) In 1986, Dr. Elizabeth Barrett-Connor published an article in The Western Journal of Medicine in which she stated: "[T]here are no studies of adequate design, duration and sample size to determine the risks and benefits of any prolonged estrogen-progestin combination in post-menopausal

women. . . . Given the high prescribing rates reported for progestin, any possible untoward effects should be quickly researched analyzed in relation to the benefits of such use." (Response, Ex. 48, at 2.)

In 1989, Wyeth held its annual symposium in Estoril, Portugal, on the long-term effects of estrogen deprivation. (Response, Ex. 52.) In an article penned in conjunction with the symposium, Dr. David B. Thomas stated that "prolonged exposure to a progestin, perhaps in the presence of estrogen, might enhance the risk [of breast cancer]." (Response, Ex. 52, at 20.) That same author also found that three studies conducted in Sweden, Great Britain, and Denmark provided some preliminary results on the risk of E+P. (Response, Ex. 52, at 21-23.) The Swedish study showed no increase in breast cancer risk among women given estrogen with an unspecified progestin for more than three years. (Response, Ex. 52, at 21.) The British study delivered a statistically non-significant result suggesting a slight increase in relative breast cancer risk (1.2) in women receiving various combinations of estrogens and progestins for four years or longer. (Response, Ex. 52, at 21.) The Danish study indicated no increase in breast cancer risk among women who received progestin with every dose of estrogen. (Response, Ex. 52, at 23.) In closing, the author called for more studies on the effects of estrogen replacement therapy "for possible carcinogenic" effects on breast tissue. (Response, Ex. 52, at 23.)

In early January 1990, Wyeth submitted an "exhaustive review of the world's literature published since 1976 examining the possible relationship between breast cancer and hormone replacement therapy" to the Division of Metabolism and Endocrine Drug Products of the FDA. (Response, Ex. 54.) Unfortunately, Mr. Scharff has only enclosed the cover page of that "exhaustive review." (Response, Ex. 54.) In the absence of that document, the court assumes that the report is the "exhaustive review" that it is purported to be.

At a February 1990 meeting of the FDA Fertility and Mental Health Advisory Committee, Dr. Linda Golden, an FDA medical officer, presented animal evidence "suggesting that exogenous estrogens as well as progestogens can produce breast cancer." (Response, Ex. 55, at 2.) Other doctors presented opposing opinions on the relationship between hormone replacement therapy and breast cancer. (Response, Ex. 55, at 2.) In the summary minutes of the meeting, the Committee posed the question, "Does the addition of progestins to estrogen therapy alter the risk of breast cancer in postmenopausal women?" (Response, Ex. 56, at 3.) The Committee responded unanimously "that there are insufficient data to answer these questions at this time." (Response, Ex. 56, at 3.)

In response to the Committee meeting, a Wyeth employee circulated a congratulatory internal memorandum stating that it was Wyeth's goal "to ensure that

this meeting was a 'non-event,' and that's exactly what happened." (Response, Ex. 57, at 1.) Further, the memorandum urged that "[w]e must position Wyeth-Ayerst as the authoritative information source on HRT. This means that we must more and more be the providers of new credible medical and scientific information concerning HRT." (Response, Ex. 57, at 1.) The memorandum closed: "Eventually the various questions that this Advisory Committee could not answer conclusively will be answered, and it is our responsibility and very much to our benefit for Wyeth-Ayerst to provide the studies, information, and insights to ensure that the answers will be accurate and balanced." (Response, Ex. 57, a 1.) In a later internal memorandum to the Premarin Team, the same Wyeth employee added: "Congratulations on the success you achieved at the recent FDA Advisory Committee meeting. We are on our way to making Premarin® a $1 billion drug." (Response, Ex. 58.)

Later that year in an internal memorandum, Wyeth Director of Regulatory Affairs Justin Victoria memorialized a meeting he had with an FDA Director and Compliance Officer. (Response, Ex. 53, at 1.) In that memo, he explained that the FDA Director and the FDA "remain[ed] unconvinced of the overall safety and effectiveness of combined estrogen/progestin therapy." (Response, Ex. 53, at 1.) The FDA Director noted that there was no approved New Drug Application for combination Premarin/progestin therapy, and that the FDA would have to approve a

full New Drug Application to allow for such a combination. (Response, Ex. 53, at 1.) The FDA Compliance Office expressed similar concerns. (Response, Ex. 53, at 2.) Mr. Victoria concluded that, "without adequate clinical data to address the benefit/risk ratio of combined estrogen/progestin therapy, [the FDA Director] and his Division will not approve such a combination." (Response, Ex. 53, at 2.) He also noted that Wyeth's "Premarin/MPA clinical program continues to progress on schedule to meet the 1992 target NDA [New Drug Application] filing." (Response, Ex. 53, at 2.)

In April 1990, epidemiologists Drs. Glass and Hoover published a report entitled Rising Incidence of Breast Cancer: Relationship to Stage and Receptor Status. (Response, Ex. 59, at 1.) Based on a review of Kaiser Permanente's population-based tumor registry, the report analyzed breast cancer incidence from 1960 to 1985. (Response, Ex. 59, at 1.) In the report, Drs. Glass and Hoover found a 131% increase in ER+ breast tumors between the mid-1970s and the mid-1980s, "*perhaps* implicating *hormonal factors* in the rising incidence of breast cancer." (Response, Ex. 59, at 1 (emphasis added).) In absolute terms, this represented a growth in ER+ cancers from 24.9 per 100,000 population in 1974-1977, to 39.9 per 100,000 population in 1978-1981, to 57.5 per 100,000 population in 1982-1985. (Response, Ex. 59, at 3.) In comparison, the total breast cancer incidence for all ages

grew from 79.3 per 100,000 population in 1970-1974, to 89.2 per 100,000 population in 1975-1979, to 100.3 per 100,000 population in 1980-1985. (Response, Ex. 59, at 2.) In the sixty and over age group, the overall breast cancer rate was much higher, 284.2 per 100,000 population in 1970-1974, 287.2 per 100,000 population in 1975-1979, and 374.6 per 100,000 population in 1980-1985. (Response, Ex. 59, at 2.) The Glass-Hoover report concluded with the hypothesis that, "[i]f ER + and ER - cancer have different etiologic factors, hormonal influences could be responsible for the differential rise in ER + breast cancer over time." (Response, Ex. 59, at 4.)

In a 1991 letter to the editor in the American Journal of Epidemiology, Drs. Grady and Ernster called for "additional data on the effect of combination hormone therapy on breast cancer risk." (Response, Ex. 60, at 4.) The letter noted that that edition of the American Journal of Epidemiology included "two large, well-conducted case-control studies that address the effects of hormone therapy on breast cancer." (Response, Ex. 60, at 1.) Drs. Grandy and Ernster found these reports to be conflicting. One found a small decrease in the relative risk of breast cancer in women

treated with E+P, while the other found a small increase in the risk of breast cancer in women treated with E+P.[12] (Response, Ex. 60, at 3.)

In June 1991, the FDA again conducted an Advisory Committee meeting to review the current status of combined hormone replacement therapy, and Wyeth again submitted a "comprehensive review of the literature regarding the effects of estrogen / progestin therapy in postmenopausal women." (Response, Exs. 61-62.) Again, Mr. Scharff has only submitted the cover page of the "comprehensive review." (Response, Ex. 61.) The Committee posited the question, "To what degree does the progestogen in HRT affect . . . the possible risk of breast cancer induced by ERT?" and responded, "The data are not yet adequate to permit an answer to this question but such information will be forthcoming." (Response, Ex. 62.)

In December 1992, Wyeth submitted a New Drug Application for conjugated estrogens and Medroxyprogesterone Acetate, covering both Prempro and Premphase. (Response, Ex. 65, at 1.)

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[12] Relative risk is defined "as the ratio of the incidence rate (often referred to as incidence) of disease in exposed individuals to the incidence rate in unexposed individuals." Federal Judicial Center, *Reference Manual on Scientific Evidence* 348 (2d ed. 2000). "The incidence rate of disease reflects the number of cases of disease that develop during a specified period of time divided by the number of persons in the cohort under study. *Thus, the incidence rate expresses the risk that a member of the population will develop the disease within a specified period of time.*" *Id.* at 348-49 (emphasis added).

In May 1993, at an industry conference attended by Wyeth officials, Dr. Linda Golden, an FDA medical officer, offered a presentation on "Quandaries in HRT Therapy." (Response, Ex. 64.) According to a Wyeth internal memorandum, Dr. Golden was concerned that E+P would not offer the same "cardioprotective benefit" to women as ERT, nor was she "comfortable with the risk/benefit ratio with respect to breast cancer and prolonged estrogen therapy." (Response, Ex. 64, at 1.) She also noted that the FDA was evaluating E+P combination therapy, and that most breast cancer studies were epidemiologic studies not based on randomized groups. (Response, Ex. 64, at 1.) Dr. Golden called for well controlled placebo randomized studies for new uses of estrogen products. (Response, Ex. 64, at 1.) In an October 1993 meeting between Wyeth and the FDA's Division of Metabolism and Endocrine Drug Products about Wyeth's New Drug Application for an E+P product, Dr. Golden expressed her concerns "about the safety of adding excess progestin, i.e. breast cancer." (Response, Ex. 65, at 7.) Therefore, she wanted assurances that Wyeth would "not exceed the lowest effective dose of MPA for the companion dose of Premarin." (Response, Ex. 65, at 7.)

In December 1994, Dr. Golden completed a Medical Officer's Review of the Prempro and Premphase New Drug Application submitted by Wyeth. (Response, Ex. 66.) In the Review, Dr. Golden recommended approval of Wyeth's New Drug

Application for both Prempro and Premphase. (Response, Ex. 66, at 74-75.) However, Dr. Golden noted her concerns with the risk of breast cancer associated with Prempro and Premphase. (Response, Ex. 66, at 7-8, 74-75.) She noted that "many more years are still needed before the relationship between HRT and breast cancer can be definitively determined." (Response, Ex. 66, at 8.) Further, because of the growing popularity of HRT use by aging "baby boom" women, she noted that the public health impact of this safety concern was increasing. (Response, Ex. 66, at 8.) Therefore, she concluded that "the true effect of HRT on breast cancer incidence and mortality must be considered the single most important safety issue concerning this class of drugs." (Response, Ex. 66, at 8.) She also noted that recent relative risk estimates for HRT and breast cancer "suggest that concomitant progestins do not reduce and may exacerbate the risk of breast cancer associated with ERT." (Response, Ex. 66, at 8.) However, Dr. Golden approved, with some modifications, Wyeth's proposed labeling of Prempro and Premphase, including the warning about the risk of breast cancer. (Response, Ex. 66, at 62-71; *see also* Ex. 67, at 4 ("The final printed labeling (FPL) must be identical to the December 20 and 30, 1994, draft labeling.").) Therefore, she recommended the Prempro and Premphase New Drug Application for approval on the condition that Wyeth "will conduct a comprehensive Phase IV investigation of breast cancer risk in users and non-users of the NDA regimens." (Response, Ex. 66, at 74.)

On December 30, 1994, the FDA approved Wyeth's New Drug Application for Prempro and Premphase, concluding "that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted draft labeling." (Response, Ex. 67, at 4.) The approval letter also referenced Wyeth's "additional Phase 4 commitment made in a December 30 telefacsimile to conduct a comprehensive investigation of breast cancer risk in users and non-users of the New Drug Application regimens at appropriate and reasonable cost." (Response, Ex. 67, at 5.)

Mr. Scharff produced evidence, however, that Wyeth did not undertake or sponsor an independent, comprehensive study of breast cancer risk associated with HRT prior to Mrs. Scharff's consumption of Prempro from 1997 to 1999. (Response, Ex. 27, at 1914; Ex. 73, at 51-58; Ex. 74, at 695; Ex. 75, at 380, 384; Ex. 76, at 339-41; Ex. 77, at 32-33; Exs. 78-79, 81, at 37-51.) Wyeth disputes this evidence, but Mr. Scharff's evidence must be credited. (Reply 35-39.)

However, Wyeth produced undisputed evidence that it submitted a proposed protocol for the Phase IV study to the FDA in 1995, and met with the FDA to review the proposal. (Reply, Exs. 51-52.) In Wyeth's minutes from a November 1995 meeting with the FDA, an FDA medical officer noted that "the initiation of any study would still be a number of years away (8-9 years)," and indicated that he had second thoughts regarding the feasibility of conducting the Phase IV trial. (Reply, Ex. 52,

at 2-3.) Further, another FDA official indicated she would note Wyeth's due diligence in meeting its post-approval commitment in spite of the delay in initiating the trial. (Reply, Ex. 52, at 3.) Ultimately, in November 1997, the FDA relieved Wyeth of its Phase IV study commitment. (Reply, Ex. 54.) The FDA concluded that Wyeth's "support for . . . prospective studies [the Women's Health Initiative and Women's International Study of Long-duration Oestrogen After Menopause] will fulfill th[e] Phase 4 commitment, and that conduct of the previously discussed case-control study is not necessary." (Reply, Ex. 54.)

2. Wyeth's Knowledge Concerning the Risk of Breast Cancer Associated with E+P

Mr. Scharff claims that the 1994 to 2002 breast cancer warnings on the Prempro label were inaccurate, and that Wyeth only corrected the breast cancer warnings after the WHI study was published.[13] (Response 38.) Mr. Scharff claims that Wyeth knew of the inaccuracies because it "learned of studies conducted by independent researchers in those years [prior to the WHI study] that showed a real breast cancer risk with E+P." (Response 38.) Because Wyeth's knowledge concerning the risk of breast cancer is central to whether it failed to warn of the risk of breast cancer while conscious that injury would likely or probably result from that

[13] The facts surrounding Wyeth's knowledge of the risk of breast cancer up to January 1999, when Mrs. Scharff was diagnosed with breast cancer and ceased taking Prempro, are examined here. *See* Part I.A.1 for the text of the pertinent Prempro breast cancer warning.

failure, the court turns to the facts surrounding Wyeth's knowledge about the risk of breast cancer.[14] *See, e.g.*, *Ex parte Capstone Bldg. Corp.*, No 1090966, 2011 WL 2164027, at *6-7 (Ala. June 3, 2011).

In August 1989, a study entitled "The Risk of Breast Cancer After Estrogen and Estrogen-Progestin Replacement" (the "Bergkvist Study") was published in the New England Journal of Medicine. The Bergkvist Study was a "prospective study of 23,244 women 35 years of age or older who had had estrogen prescriptions filled in the Uppsala region of Sweden."[15] (Response, Ex. 88, at 1.) "During the follow-up period (mean, 5.7 years) breast cancer developed in 253 women." (Response, Ex. 88, at 1.) 208 of these women had consumed some form of estrogen or E+P, while 45 reported no use of estrogens despite their prescription. (Response, Ex. 88, at 3.) The expected number of breast cancers in the cohort was 222.5, giving a relative risk of breast cancer for all of the participants of 1.1 (95% confidence interval, 1.0 to 1.3).

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[14] Mr. Scharff also produced evidence concerning Wyeth's marketing efforts, "ghost-writing," and other publicity efforts to combat negative studies from 1994 to 1999. (Response 38-49; *see also* Response 49-57 (Wyeth's distortion of the risk benefit profile for E+P).) However, Mr. Scharff has not adequately explained how this evidence is relevant to the material issue of how Wyeth wantonly failed to warn Dr. Reiland of the risk of breast cancer associated with Prempro. Further, there is no evidence that Dr. Reiland or Mrs. Scharff read or relied on any of those articles or studies. (*See supra* Part I.A; Reply 40-42.)

[15] The relative risk of breast cancer was calculated according to the following ratio: (the number of observed breast cancer cases) / (the number of breast cancer cases expected). The expected breast cancer calculation was based on the risk of breast cancer among the population of women in the Uppsala health care region that were not included in the study cohort (4213 breast cancer cases in 2,064,293 person-years of observation). (Response, Ex. 88, at 2.)

Though the study consisted primarily of women on ERT, it also included women who consumed some form of E+P. (Response, Ex. 88, at 2.) With respect to women who consumed only E+P, the study found a relative risk of breast cancer of 4.4 (95% confidence interval: .9 to 22.4) among long-term users, those patients with more than six years of use. (Response, Ex. 88, at 3.) For women who had consumed E+P for less than six years, the relative risk of breast cancer was less than 1, however. (Response, Ex. 88, at 3 (Table 3) (less than 6 months use, relative risk .5 (95% confidence interval: .2-1.8); 7 months to 36 months use, relative risk .7 (95% confidence interval: .3-1.3); 37-72 months use, relative risk .9 (95% confidence interval, .3-2.6)).)

In comparison, women who reported no estrogen consumption despite their prescription nevertheless had a relative risk of breast cancer of 1.6 (95% confidence interval, 1.1-2.1). In their discussion section, the authors wrote:

> Overall, we noted a 10 percent increase in the relative risk of breast cancer in 23,244 women for whom estrogens were prescribed for symptoms of menopause. . . . Our study found that the addition of progestin offered no protection against the development of breast cancer. This observation raises concern about the long-term treatment with a combination of estrogens and progestins that has been proposed for widespread use as prophylaxis against osteoporosis in menopausal women. . . . Finally, whereas a number of the relative risks and associated trends in this investigation were statistically significant, the number of observations on which they are based is relatively small. Some findings could be due to chance and need to be considered in the context of the results in other studies. In particular, the higher relative risks associated with the use of the combination regimen were not statistically different from the risks of estrogen use alone. Although this

> result is somewhat worrisome, we currently interpret it as indicating a lack of evidence that the concomitant use of progestin reduces the excess risk of breast cancer associated with long-term estrogen use. However, further research must also investigate the possibility that the addition of progestins to estrogen therapy may increase the risk of breast cancer.

(Response, Ex. 88, at 4-5.) In response to the study, Wyeth instructed its sales team to "Take the time to read the study," but "[u]nder no circumstances should you initiate discussions concerning this study." (Response, Ex. 90.) However, "[i]f questioned about this issue, your response should be factual." (Response, Ex. 90.)

In 1994, a Wyeth internal memorandum summarized a telephone conference between Suzanne Joyner, and Dr. Trudy Bush, a Wyeth consultant. (Response, Ex. 87.) In that memo, Ms. Joyner memorialized Dr. Bush's report that "data from Katherine Fletcher at the National Cancer Institute, in a retrospective study conducted in the 70's [sic] [,] saw an increased risk of breast cancer in women on HRT any dose [sic], as compared to ERT." (Response, Ex. 87.) Dr. Bush also reported that "[t]his data is not sufficient to rule out the use of estrogen/progestogen cyclic or combined therapy." (Response, Ex. 87.)

In 1995, Dr. Graham Colditz published an article entitled "The Use of Estrogens and Progestins and The Risk of Breast Cancer in Postmenopausal Women" in the New England Journal of Medicine. (Response, Ex. 94.) This article was a follow-up on the previous Nurse's Health Study that began in 1976 with

questionnaires sent to 121,700 female registered nurses, and continued with follow-ups sent every two years. (Response, Ex. 94, at 2.) The analysis of the participants of the Nurse's Health Study was extended to 1992 to address unresolved issues including "the risks associated with estrogen plus progestins." (Response, Ex. 94, at 2.) The article summary opened, "The effect of adding progestins to estrogen therapy on the risk of breast cancer in post-menopausal women is controversial." (Response, Ex. 94, at 2.)

The study found a significant elevation in the risk of breast cancer among participants using conjugated estrogens alone (adjusted relative risk, 1.32; 95% confidence interval, 1.14 to 1.54), and estrogens plus progestin (adjusted relative risk, 1.41; 95% confidence interval, 1.15 to 1.74), as compared to those who had never used such therapy. (Response, Ex. 94, at 3.) In 725,550 person-years of follow-up, the study identified 1935 cases of invasive breast cancer among 69,586 post-menopausal women. (Response, Ex. 94, at 3.) 972 of those cases involved women who had never used hormone therapy, accounting for 374,197 person-years of follow-up; and the remaining 963 cases involved women who were taking or had taken some form of hormone therapy, accounting for 351,353 person-years of follow-up. (Response, Ex. 94, at 3-4.) The study found that "[t]he increase in [breast cancer] risk was most pronounced among women over the age of 55 and was largely limited to the

women who had used hormone therapy for five or more years." (Response, Ex. 94, at 4.) The study concluded:

> Our data indicate that the addition of progestins to post-menopausal estrogen therapy does not reduce the risk of breast cancer. Estrogen alone, estrogen plus progestin, and progestins alone all appear to raise the risk of breast cancer. The significant increase in the risks of breast cancer and of death due to breast cancer among postmenopausal women over 55 who are currently taking hormones and who have used this therapy for five or more years suggests that the risks and benefits of hormone therapy among older women should be carefully assessed.

(Response, Ex. 94, at 5.)

In 1996, Dr. Steven Cummings published an article entitled "Bone Mineral Density Predicts the Risk of Breast Cancer in Older Women." (Response, Ex. 101, at 1.) In that article, Dr. Cummings explained that "[b]oth breast cancer and bone mineral density (BMD) are related to exposure to estrogens." (Response, Ex. 101, at 1.) The study found that the "age-related relative risk of breast cancer increased by 30 to 40% for each standard deviation increase in distal radius BMD: relative risk 1.40; 94% confidence interval, 1.16 to 1.68." (Response, Ex. 101, at 1.) Dr. Cummings also posited that "[o]ur findings suggest that the risk of breast cancer associated with hormone replacement therapy may have been substantially underestimated since osteoporosis is a primary indication for its use." (Response, Ex. 101, at 1.)

In October 1997, the Collaborative Group on Hormonal Factors in Breast Cancer published an article in The Lancet titled "Breast Cancer and Hormone Replacement Therapy: Collaborative Reanalysis of Data from 51 Epidemiological Studies of 52,705 Women with Breast Cancer and 108,411 Women Without Breast Cancer." (Response, Ex. 108, at 1 (the "Collaborative Group Study").) The Collaborative Group's main finding was that the "risk of breast cancer is increased in women using HRT and increases with increased duration of use, but that this excess risk is reduced after use ceases and has largely, if not completely, disappeared after about 5 years." (Response, Ex. 108, at 8.) Among current users of HRT, the Collaborative Group found a relative risk of breast cancer of 1.21. (Response, Ex. 108, at 6.) Among women who had ever used HRT, the Collaborative Group found a relative risk of breast cancer of 1.14. (Response, Ex. 108, at 6.)

Most importantly for the purposes of this motion, the Collaborative Group also expressed these numbers in terms of the actual incidence of breast cancer as a result of continuous use of HRT by post-menopausal women. (Response, Ex. 108, at 11 (*See* Table 3 and Figure 9).) First, in North America and Europe in the mid-1980s, the cumulative incidence of breast cancer between the ages of 50 and 70 for those who had never used HRT was about 45 per 1000 women. (Response, Ex. 108, at 11.) Measured against that baseline, the Collaborative Group found that "[u]se of HRT for

5 years is associated with an estimated cumulative excess of 2 (95% CI 1-3) breast cancers for every 1000 users[;] use for 10 years with a cumulative excess of 6 (3-9) for every 1000 users; [and] use for 15 years is associated with a cumulative excess of 12 (5-20) breast cancers for every 1000 users." (Response, Ex. 108, at 11.)

For 55-year-old women, the age of Mrs. Scharff at the time of her Prempro prescription, the cumulative incidence of breast cancer among those who had never used HRT was 27 per 1000 women. (Response, Ex. 108, at 11 (Table 3).) For 55-year-old women who had begun using HRT at 50 (5 years of use), the cumulative incidence of breast cancer increased from 27 per 1000 women to 28 per 1000 women. (Response, Ex. 108, at 11 (Table 3).) The Collaborative Group Study did note, however, that the average date of breast cancer diagnosis for the women in the study was 1985, when the type of HRT in predominant use was estrogen only, with only 12% of the women having mainly used an E+P combination.[16] (Response, Ex. 108, at 11.) Table 3 and Figure 9 from the Collaborative Group Study are reproduced below:[17]

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[16] The lack of E+P data in this 1997 study is noted, but that disparity is irrelevant for purposes of this opinion, which turns on Wyeth's knowledge of the risk of breast cancer from 1997 to 1999 when Prempro was prescribed to Mrs. Scharff.

[17] Collaborative Group on Hormonal Factors in Breast Cancer, *Breast Cancer and Hormone Replacement Therapy: Collaborative Reanalysis of Data from 51 Epidemiological Studies of 52,705 Women with Breast Cancer and 108,411 Women Without Breast Cancer*, 350 The Lancet 1047, 1057 (1997).

Up to age (years)	Cumulative incidence per 1000 women						
	Never-users*	Use beginning at age 50†			Use beginning at age 55†		
		Use for 5 years	Use for 10 years	Use for 15 years	Use for 5 years	Use for 10 years	Use for 15 years
50	18	18	18	18	..	..	..
55	27	28	28	28	27	27	27
60	38	40	41	41	39	39	39
65	50	52	56	57	52	53	53
70	63	65	69	75	65	69	70
75	77	79	83	89	79	83	90

*Based on incidence rates per 1000 for breast cancer intermediate between UK and USA incidence rates in mid-1980s.[1]
†With assumption that relative risk within current users and those who ceased use 1–4 years before increases by 2·3% for each year of use, and that all women are same age at menopause.

Table 3: **Estimated cumulative incidence of breast cancer in 1000 women in North America or Europe associated with postmenopausal use of HRT for various durations, beginning at various ages**

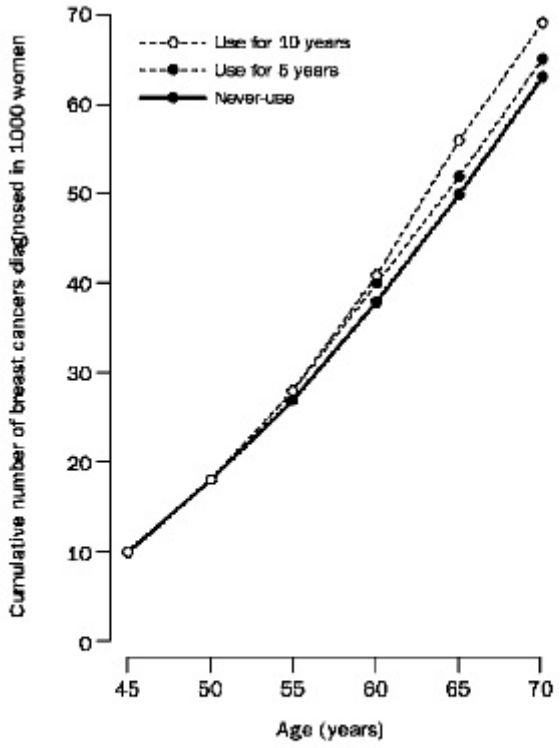

Figure 9: Estimated cumulative number of breast cancers diagnosed in 1000 never-users of HRT, 1000 users of HRT for 5 years, and 1000 users of HRT for 10 years
Estimated numbers for 1000 women in Europe or North America, with assumption that HRT use began at age 50.

In June 1998, Dr. Graham Colditz published "Relationship Between Estrogen Levels, Use of Hormone Replacement Therapy, and Breast Cancer" in The Journal of the National Cancer Institute. (Response, Ex. 115.) In the article, Dr. Colditz posed the clinical question, "Does long term use of hormone replacement increase risk of breast cancer and, if so, how soon after use has begun does risk increase?" (Response, Ex. 115, at 1.) Throughout the article, Dr. Colditz relied heavily on the data and conclusions of the Collaborative Group Study and his 1995 Nurse's Health Study, while also briefly mentioning the Bergkvist Study. (Response, Ex. 115, at 1-6.) He concluded that "existing evidence supports a causal relationship between use of estrogens and progestins, levels of endogenous estrogens, and breast cancer incidence in post-menopausal women. Hormones may act to promote the late stages of carcinogenesis among postmenopausal women to facilitate the proliferation of malignant cells." (Response, Ex. 115, at 1.)

However, Dr. Colditz also noted that the decision whether to prescribe E+P in light of the risk of breast cancer was not a simple one, because of the then-understood net mortality-reducing benefits of E+P. (Response, Ex. 115, at 7.) He posed the dilemma in balancing the risk of breast cancer with the then-understood benefits of E+P:

> Women who used postmenopausal hormones for 10 or more years had a 20% reduction in mortality that was statistically significant. This benefit of hormones was most pronounced among women who were at higher risk for cardiovascular disease. However, to achieve a reduction in mortality, some women within the population will pay the price of a breast cancer that they would not otherwise have developed. That is to say, some individuals experience a disadvantage as a result of an attempt to improve the overall health of the population. Thus, the action that will benefit public health and the individual's best choice may differ. Further work is needed to improve our understanding and communication of these considerations.

(Response, Ex. 115, at 7.)

In 2002, the Women's Health Initiative changed the menopause market, caused the FDA to require Wyeth to make substantial changes to the breast cancer warnings on the Prempro label, and changed the E+P product actually marketed by Wyeth. (Response 17-18.) Because Mr. Scharff relies on the WHI studies to show the inadequacies of the pre-WHI Prempro label as it relates to the breast cancer risk, the statistical results of this study are pertinent to the factual issue of likely or probable injury.[18]

The primary conclusion of the WHI study was that the "[o]verall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2 year follow-up among healthy postmenopausal US women." (Response, Ex. 16, at 1.)

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[18] *See* Part I.A.2 for discussion of the WHI study's effect on Dr. Reiland's understanding of the risk of breast cancer associated with E+P.

The WHI researchers also concluded that the "risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of [coronary heart disease]." (Response, Ex. 16, at 1.) The study found that women who had consumed E+P had a relative risk of developing breast cancer of 1.26 (95% confidence interval, 1.00-1.59).[19] (Response, Ex. 16, at 7.) Among the study participants, there were 166 invasive breast cancers among the 8506 women taking E+P (1.95% overall breast cancer rate), and 124 invasive breast cancers among the 8102 women taking the placebo (1.53% overall breast cancer rate). (Response, Ex. 16, at 7 (Table 2).) In terms of annualized percentages, .30% of the placebo group developed breast cancer per year compared to .38% of E+P group.[20] (Response, Ex. 16, at 7 (Table 2).)

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[19] Wyeth notes that the 2003 Chlebowski article *Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women: The Women's Health Initiative Randomized Trial* adjusted the WHI based relative risk of breast cancer down to 1.24. (Reply 26 & Ex. 11.) Likewise, in that breast cancer specific follow-up on the WHI study, there were 199 invasive breast cancers among 8506 women taking E+P (2.33% breast cancer rate), and 150 invasive breast cancers among 8102 women taking placebo (1.85% breast cancer rate). Though the differences between the studies are small, the court relies on the study cited by Mr. Scharff.

[20] Dr. Colditz testified that the relative risk difference of 1.24 in the 2003 Chlebowski article "in this particular population translates to a risk difference of . . . 8/100ths of one percent." (Reply, Ex. 27 at 392-93.) That statistical explanation applies equally to the annualized percentages presented in the 2003 Cheblowski article (Reply, Ex. 11, at 3249 (Table 3)) and the 2002 JAMA article (Response, Ex. 16, at 7 (Table 2)).

Finally, Mr. Scharff's evidence also includes an unattributed spreadsheet that purports to show that 32 of the 43 pre-WHI studies concerning E+P found "Increased Breast Cancer Risk" versus "NO Breast Cancer Risk." (Response 41 & Ex. 91.) In *Torkie-Tork v. Wyeth*, a breast cancer hormone therapy case, District Judge T.S. Ellis, III confronted the same argument, reviewed the statistical data cited in each of the cases in light of statistical principles, construed that review in the light most favorable to the plaintiff, and found that 23 of the 43 pre-WHI breast cancer studies did not in fact show a statistically significant association between breast cancer and the use of estrogen replacement theory.[21] 739 F. Supp. 2d 895, 902-904 (E.D. Va. 2010) (discussing statistical principles and citing Federal Judicial Center, *Reference Manual on Scientific Evidence* 360 (2d ed. 2000)). The court finds that review persuasive.

[21] Notably, it appears that the plaintiff's counsel in *Torkie-Tork* included all of the 43 pre-WHI studies in a consolidated exhibit to permit the district court to review all of the evidence. *Torkie-Tork*, 739 F. Supp. 2d at 903 (all the cited studies, save one, were consolidated in Exhibits 71H-LL). In this case, Mr. Scharff's Exhibit 91 consists only of an excel spreadsheet listing the "Author/Publication," the "Date," and a binary categorization of each article as "Increased Breast Cancer Risk" or "NO Breast Cancer Risk." (Response, Ex. 91.) No other data is provided, nor are the pertinent parts of the articles attached. The court is without evidence to verify or adopt Plaintiff's unattributed factual position. *See* Federal Judicial Center, *Reference Manual on Scientific Evidence* 55 (2d ed. 2000) ("[A] declaration containing a mere conclusory statement of opinion by an expert unsupported by facts does not suffice to raise a triable issue.").

3. Wyeth's Distortion of the Risk/Benefit Ratio

Finally, Mr. Scharff produced evidence regarding Wyeth's alleged distortion of doctors' risk/benefit analysis through its marketing representatives, ghost-written medical articles, Dear Doctor letters, promotional materials, and conferences. (Response 49-56.) The evidence has been reviewed, but as will be seen below, it is not probative of Wyeth's knowledge of the likely or probable risk of breast cancer caused by E+P therapy. It is, therefore, not relevant to Mr. Scharff's wanton failure to warn claim. Nor has Mr. Scharff produced evidence that Dr. Reiland relied on any of this "distorted" evidence when he prescribed Prempro to Mrs. Scharff in 1997.

II. DISCUSSION

The Discussion proceeds in two parts. In Part A, the analysis begins with the lack of genuine issues of material fact supporting Mr. Scharff's wanton failure to warn claim. In Part B, the court briefly dispenses with Mr. Scharff's wanton design claim.

A. Mr. Scharff's Wanton Failure to Warn Claim

In Alabama, the term "wantonness" is statutorily defined, for purposes of punitive damages, as "[c]onduct which is carried on with a reckless or conscious disregard of the rights or safety of others." Ala. Code § 6-11-20(b)(3). The contours of a cause of action arising out of wanton conduct, however, are delineated by

common law. The Alabama Supreme Court defined the cause of action for wantonness as:

> the conscious doing of some act or the omission of some duty, while knowing of the existing conditions and being conscious that, from doing or omitting to do an act, injury will likely or probably result. To prove wantonness, it is not essential to prove that the defendant entertained a specific design or intent to injure the plaintiff.

Ex parte Capstone, 2011 WL 2164027, at *6 (citing *Ala. Mut. Ins. Co. v. Roush*, 723 So. 2d 1250, 1256 (Ala. 1998) (internal citations omitted)). "The 'knowledge' [of risk of injury] of the defendant is 'the *sine qua non* of wantonness.'" *Blakley v. Johnson*, No. 2090507, 2010 WL 4262303, at *7 (Ala. Civ. App. Oct. 29, 2010) (bracketed comments in *Blakley*) (quoting *Norris v. City of Montgomery*, 821 So. 2d 149, 156 n.9 (Ala. 2001)). The defendant's knowledge "may be proved by showing circumstances from which the fact of knowledge is a reasonable inference; it need not be proved by direct evidence." *Hamme v. CSX Transp., Inc.*, 621 So. 2d 281, 283 (Ala. 1993).

The degree to which the defendant either knew about, should have known about, or was conscious of the risk is central to a wantonness claim. "Wantonness is not merely a higher degree of culpability than negligence." *Ex parte Capstone*, 2011 WL 2164027, at *6 (internal quotation marks and citation omitted). "[N]egligence and wantonness are qualitatively different tort concepts." *Id.*; *Ferguson v. Baptist Health Sys., Inc.*, 910 So. 2d 85, 92 (Ala. 2005). Wantonness involves an "act done

or omitted with knowledge of the *probable consequence* and with reckless disregard of such consequence." *Ex parte Capstone*, 2011 WL 2164027, at *6 (emphasis changed). On the other hand, negligence consists of "intentionally doing an act with knowledge that it contains a risk of harm to others," but for an actor "to be reckless [he] must recognize that his conduct involves a risk substantially greater in amount than that which is necessary to make his conduct negligent." Restatement (Second) of Torts § 500 (comment g) (cited in *Ex parte Capstone*, 2011 WL 2164027, at *7 n.3). "The difference between reckless misconduct and conduct involving only such a quantum of risk as is necessary to make it negligent is a difference in the degree of the risk, but this difference of degree is so marked as to amount substantially to a difference in kind." Restatement (Second) of Torts § 500 (comment g) (quoted in *Ex parte Capstone*, 2011 WL 2164027, at *7 n.3).[22]

> While it may be difficult to define the exact point at which the probability of harm is sufficient to support a jury's finding of

[22] The difference in the degree of risk necessary for wantonness was also emphasized by the concurring justices in *Ex parte Capstone*. 2011 WL 2164027, at *14 ("'It is enough [for wantonness] that [the defendant] realizes or, from the facts which he knows, should realize that there is a *strong probability* that harm may result, even though he hopes or even expects that his conduct will prove harmless.'") (Murdock, J., concurring specially) (quoting Restatement (Second) of Torts § 500 (1965) (comment f)); *id.* ("[R]eckless misconduct results when a person, with no intent to cause harm, intentionally performs an act so unreasonable and dangerous that he or she knows or should know it is *highly probable* that harm will result.") (Murdock, J., concurring specially) (quoting 57A Am. Jur. 2d Negligence § 276 (2004)) (emphasis added); *id.* at *15 ("[T]he defendant who acts in the belief or consciousness that the act is causing *appreciable risk of harm* to another may be negligent, and *if the risk is great* the conduct may be characterized as reckless or wanton . . . .") (Murdock, J., concurring specially) (quoting W. Page Keeton *et al.*, *Prosser & Keeton on the Law of Torts* § 8, p. 36 (4th ed. 1984)) (emphasis changed); *see also id.* at *16 (Main, J., concurring specially).

> wantonness, courts and juries must attempt to discern that line in light of the fact that wantonness is distinct from negligence, and punitive damages are meant "to punish [the defendant] for his outrageous conduct and to deter him and others like him from similar conduct in the future."

Salter v. Westra, 904 F.2d 1517, 1527 (11th Cir. 1990) (quoting Restatement (Second) of Torts § 908(1) (1979)); *see also Richards v. Michelin Tire Corp.*, 21 F.3d 1048, 1057-58 (11th Cir. 1994).

The analysis proceeds in three sections. Part II.A.1 begins with whether Mr. Scharff has produced evidence that breast cancer was a likely or probable injury for women taking E+P. Part II.A.2 turns to whether Mr. Scharff has produced evidence that Wyeth knew, should have known, or was recklessly indifferent to the likely or probable risk of breast cancer associated with E+P. Part II.A.3 concludes with analysis of whether Mr. Scharff has created a genuine issue of material fact that the Prempro breast cancer warning provided to Dr. Reiland was wantonly inadequate.

1. No Genuine Issue of Material Fact that Breast Cancer Was a Likely or Probable Injury from Prempro Consumption

Mr. Scharff argues that Wyeth had knowledge that "E+P users were developing breast cancer" and "Wyeth learned of studies conducted by independent researchers in [the years prior to the 2002 WHI study] that showed a real breast cancer risk with

E+P." (Response 23, 38.) He also argues that Alabama case law supports imposition of punitive damages to punish a defendant for wanton conduct based on the common element of "the defendant's knowledge of the potential injury or harm that could result from the defendant's acts or failure to act." (Response 20.)[23] Wyeth replies that it could not have been conscious that the risk of developing breast cancer was likely or probable, because the risk of breast cancer associated with E+P, as identified in the WHI study, is too small to say that breast cancer is likely.

In *Toole v. McClintock*, 999 F.2d 1430 (11th Cir. 1993) ("*Toole I*"), the Eleventh Circuit explained that under Alabama law, "[w]antonness means knowledge that an act or failure to act does not *merely increase risk of injury*, but that the *act makes injury 'likely' or 'probable*.'" *Id.* at 1435 (emphasis added). In that case, the plaintiff received breast implants from a surgeon. Scar tissue later accumulated and contracted around her implants, and she returned to that surgeon seeking treatment. *Id.* at 1431. The surgeon treated the hardness by performing a "closed capsulotomy," a procedure in which the surgeon compresses the affected breast to rupture the scar tissue. *Id.* When the plaintiff's surgeon performed the closed capsulotomy, the

[23] This argument is unpersuasive because it ignores that a wantonness claim requires a demonstration of a likely or probable risk of injury. The cases cited by Mr. Scharff do not eliminate this requirement. (Response 20-21.)

procedure ruptured her breast implants, causing her serious injuries. *Id.* She sued the manufacturer of the implants and others, claiming that they had negligently and wantonly failed to adequately warn her of the risk associated with the implants. *Id.* at 1432, 1435.

The case was tried to a jury, and the jury returned punitive damages against the manufacturer on the wanton failure to warn claim. *Id.* at 1432, 1435. The district court upheld the award of punitive damages, finding that the evidence showed "'the company had knowledge that the implants were likely to rupture when closed capsulotomies were performed.'" *Id.* at 1435 (quoting the district court record). The Eleventh Circuit vacated the punitive damages award, in part because the evidence "showed that the *actual incidence* of implant ruptures from closed capsulotomies is probably *slightly less than one percent*." *Id.* (emphasis added). The court explained that, although implant rupture can be serious when it occurs, "rupture is no '*likely*'

event, *even for patients undergoing closed capsulotomies*." *Id.* (emphasis added).[24] In relying on the one percent figure, the Eleventh Circuit also noted that the pertinent statistic for the wantonness risk analysis is the likelihood of the actual injury suffered by the plaintiff, not the overall rate of complications associated with the defendant's product. *Id.* at 1435 n.13.

Mr. Scharff claims that *Toole I* is factually distinguishable from this case, but otherwise does not directly address the wantonness requirement that the risk of injury is likely or probable, nor does he address *Toole I*'s reasoning on that point. (Response 22-23.) Wyeth argues that "the risk [of breast cancer] is too small to say

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[24] *Toole I* stands in contrast to the reasoning of *Scroggin v. Wyeth*, 586 F.3d 547 (8th Cir. 2009), where the Eighth Circuit allowed the issue of punitive damages to go to the jury on the plaintiff's malicious failure to warn claim. (*See* Response 9-10.) *Scroggin* was decided under Arkansas law, which allows punitive damages when the defendant "'knew or ought to have known . . . that his or her conduct would naturally and *probably* result in injury or damage and that he or she continued the conduct with malice or in reckless disregard of the consequences from which malice may be inferred.'" *Scroggin*, 586 F.3d at 571 (quoting Ark. Code. Ann. § 16-55-206) (emphasis added). Reviewing the evidence in that case, which is similar to the evidence in this case, the court concluded that "there was sufficient evidence upon which a jury could conclude that Wyeth acted with reckless disregard to the *risk of injury*." *Scroggin*, 586 F.3d at 573 (emphasis added). Notably, the Eighth Circuit's analysis of the relevant evidence and Arkansas law ignored the probability of injury and defendant's knowledge of probable risk requirements in the plain language of the Arkansas statute. *See Scroggin*, 586 F.3d at 571-573 (no discussion of probability of injury or actual incidence of breast cancer in determining that the plaintiff's evidence was sufficient to support a jury question on punitive damages).

Toole I relied on and analyzed the totality of Alabama's definition of wantonness, including the "probable" or "likely" risk of injury requirement, and importantly is binding precedent, unlike *Scroggin*. Accordingly, the court relies on *Toole I*.

that breast cancer was (or is) a likely event[,]" and therefore he "cannot meet *Toole I*'s 'likely' requirement." (Reply 27.) Wyeth has the better argument.

Mr. Scharff's evidence is insufficient to create a genuine issue of material fact that breast cancer is a likely or probable event for those consuming Prempro. Though the WHI study reported that E+P consumption increased the relative risk of invasive breast cancer by 26% over the background risk exhibited by the control group, that increased risk resulted in an actual incidence of breast cancer of 1.95% for E+P consumers during the life of the study.[25] Viewing the evidence in the light most favorable to Mr. Scharff by assuming that E+P consumption actually caused every additional breast cancer in the E+P group beyond the background incidence of breast cancer,[26] the court finds that the actual incidence of invasive breast cancer attributable

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[25] *See supra* note 12 for the definition of "relative risk."

[26] Viewing the evidence in the light most favorable to the plaintiff, the court assumes that E+P caused every additional invasive breast cancer beyond the background risk rate reported in all of the studies discussed in this opinion. *See, e.g.*, Federal Judicial Center, *Reference Manual on Scientific Evidence* 384 (2d ed. 2000) ("The threshold for concluding that an agent was more likely than not the cause of an individual's disease is a relative risk greater than 2.0. . . . When the relative risk reaches 2.0, the agent is responsible for an equal number of cases of disease as all other background causes. Thus, a relative risk of 2.0 (with certain qualifications noted below) implies a 50% likelihood that an exposed individual's disease was caused by the agent."). However, that causal assumption should not be mistaken for a ruling on the parties' general and specific causation arguments, which need not be reached in this opinion.

to E+P was .42%.[27] Breast cancer was no likely or probable event for those women who consumed E+P in the WHI study. Even if the court were to attribute all of the invasive breast cancers in the E+P group to E+P consumption, thereby ignoring the inherent risk of breast cancer faced by all post-menopausal women (as represented by the 1.53% breast cancer rate in the placebo group), the actual incidence of breast cancer in the E+P group was 1.95%. And, even construing the evidence through that heavily jaundiced lens, far beyond the light most favorable to the plaintiff requirement, the actual incidence of breast cancer remains too small as a matter of law for a reasonable jury to find that breast cancer was a likely or probable event for women undergoing E+P treatment.

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[27] (.153 background breast cancer rate * 8506 women taking E+P) = 130.18 background invasive breast cancers. (166 E+P breast cancers - 130 background cancers) = 36 additional invasive breast cancers out of 8506 women. (36 additional breast cancers / 8506 women taking E+P) = .42% actual incidence of additional invasive breast cancers experienced by the E+P group. Or more simply: (1.95% E+P group breast cancer rate - 1.53% placebo breast cancer rate) = .42% actual incidence of additional invasive breast cancers experienced by the E+P group during the life of the WHI study.

Applying the results of the WHI study to women who had taken Prempro for the eight-year life of the drug at the time the study was published yields a similarly small actual incidence of breast cancer. For women consuming E+P for 8 years, the actual incidence of invasive breast cancers would be 3.04%. ((8 years * .38% annual incidence of invasive breast cancer) = 3.04%) For women consuming the placebo, the actual incidence of invasive breast cancer would be 2.4%. ((8 years * .30% annual incidence of invasive breast cancer) = 2.4%) Thus, the actual incidence of additional invasive breast cancers faced by the E+P group after eight years would be .64%. (*See* Response, Ex. 16, at 7 (Table 2); *cf.* Response, Ex. 16, at 10 (Table 4) (relative risk of invasive breast cancer for "Year 6 and Later" E+P group was actually 1.12, less than the 1.26 figure the annualized breast cancer incidence percentages were based on).)

If the court were examining this evidence under negligence and negligence's far less rigorous standard of foreseeability, a jury question would have resulted. *See* Part II.A. However, Mr. Scharff's negligence claims are time-barred, as found in the court's prior Order, and, thus, the negligence standard is inapplicable. Given Mr. Scharff's evidence, and applying the plain meaning of "likely," "probable," "risk substantially greater in amount than that which is necessary [for negligence]," "strong probability," "highly probable," and "the risk is great," there is no genuine issue of material fact tending to show that breast cancer was a likely or probable result of Prempro consumption.[28]

2. No Genuine Issue of Material Fact that Wyeth Knew Breast Cancer Was a Likely or Probable Injury from Prempro Consumption

In Part I.A, the analysis turned on whether Mr. Scharff had produced evidence sufficient to show a genuine issue of material fact on the key question of whether the risk of breast cancer is likely or probable from E+P consumption. In that analysis, the court purposefully ignored the *sine qua non* of wantonness, Wyeth's knowledge, and

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[28] "'[L]ikely' is defined as '[l]ogically or expectedly about to occur; imminent.'" *Henderson v. Ala. Power Co.*, 627 So. 2d 878, 903 (Ala. 1993) (abrogated on other grounds by *Ex parte Apicella*, 809 So. 2d 865, 874 (Ala. 2001) (Houston, J., dissenting) (quoting *The American Heritage Dictionary of the English Language*, 757 (1969)). "'[P]robably' is defined as '[m]ost likely; in all probability; presumably.'" *Id.* (quoting *The American Heritage Dictionary of the English Language*, 1043 (1969)); *see also* Part II.A & n.22.

instead looked purely at the risk of injury based on Mr. Scharff's evidence from the landmark WHI study. The lack of evidence that breast cancer is a likely or probable injury from Prempro consumption is sufficient alone to dispose of Mr. Scharff's wantonness claims. In the interest of completeness, however, the court (assuming *arguendo* that Mr. Scharff established the risk of injury) now examines whether Mr. Scharff has produced a genuine issue of material fact that Wyeth either knew or was recklessly indifferent to the risk that breast cancer would likely or probably result from its failure to adequately warn of the risk of breast cancer associated with Prempro.

The knowledge inquiry turns on what Wyeth knew, or should have known, about the risk of breast cancer associated with Prempro before January 1999, when Mrs. Scharff was diagnosed with breast cancer. Mr. Scharff argues that Wyeth knew of inaccuracies in the Prempro label and of the risk of breast cancer associated with Prempro during this period because it "learned of studies conducted by independent researchers in those years [prior to the WHI study] that showed a *real* breast cancer risk with E+P." (Response 38 (emphasis added).) Mr. Scharff's evidence shows that Wyeth either knew about or should have known about all of the studies cited in the Response. The court has carefully reviewed the pre-1999 ERT and HRT breast

cancer studies provided by Mr. Scharff. Review of these studies shows that no reasonable jury could find that, as of January 1999, Wyeth knew or should have known that breast cancer was a likely or probable result of its failure to adequately warn of the risk of breast cancer.

To begin, the 1989 Bergkvist Study is insufficient to establish a genuine issue of material fact on Wyeth's knowledge of a likely or probable injury for three reasons. First, its finding of a relative risk of breast cancer of 4.4 for women who consumed E+P for over six years was not statistically significant. The 95% confidence interval for that relative risk calculation was .9 to 22.4, and it thus included a relative risk of 1.0. Federal Judicial Center, *Reference Manual on Scientific Evidence* 389 (2d ed. 2000) ("Where the confidence interval contains a relative risk of 1.0, the results of the study are not statistically significant."). Second, it also reported a negative relative risk of breast cancer for E+P consumption for less than six years, though those findings were also not statistically significant. Though the Bergkvist study was important and called for further research into the "possibility that the addition of progestins to estrogen therapy may increase the risk of breast cancer," its results concerning the breast cancer risk for E+P consumption were statistically inconclusive and contradictory on the overall temporal relative risk of breast cancer. The

Bergkvist study is insufficient to create a genuine issue of material fact that Wyeth knew or should have known that breast cancer was a likely or probable result of Prempro consumption.

Next, the 1995 Nurse's Health Study includes no data tending to show that breast cancer was a likely or probable result from E+P consumption. Though the study did conclude that E+P "appear[s] to raise the risk of breast cancer," the increase observed in that study did not result in an actual incidence of breast cancer approaching a likely or probable result. The study found an annualized incidence of breast cancer of .25% for women who had never taken hormone replacement therapy, .27% for women who were taking or had taken hormone replacement therapy, and .31% for the subset of women currently taking hormone replacement therapy.[29] Again assuming causation for the additional breast cancers in the group that was currently taking E+P, the study found a .06% increase in the actual incidence of breast cancers per year. In a group of 10,000 women consuming E+P, that would mean an actual incidence of 6 additional breast cancers per year over the background annual

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[29] Annualized actual incidence of breast cancer for non-HRT takers: (972 cases/374,197 years of follow-up) = .25%.

Annualized actual incidence of breast cancer for current or former HRT takers: (963 cases/351,353 years of follow-up) = .27%.

Annualized actual incidence of breast cancer for current HRT takers: (513 cases/163,204 years of follow-up) = .31%. (*See* Response, Ex. 94, at 3-4 (Table 2).)

incidence of breast cancer (25) faced by all post-menopausal women. Though that breast cancer risk may be real, no reasonable jury could find that such an injury was likely or probable, or that it put Wyeth on notice that such a result was likely or probable.

Another study, the 1997 Collaborative Group Study, also shows that the actual incidence of breast cancer for E+P consumers was not a likely or probable event. The Collaborative Group Study found that "[u]se of HRT for 5 years is associated with an estimated cumulative excess of 2 (95% CI 1-3) breast cancers for every 1000 users[;] use for 10 years with a cumulative excess of 6 (3-9) for every 1000 users; [and] use for 15 years is associated with a cumulative excess of 12 (5-20) breast cancers for every 1000 users." (Response, Ex. 108, at 11.) Further, "[u]se of HRT for about 4 years would therefore result in one extra breast cancer being diagnosed in every 1000 users, and use for about 13 years would result in one extra cancer being diagnosed in every 100 users." (Response, Ex. 108, at 11.) Looking at the extreme case, a woman consuming hormone replacement therapy for 15 years, the actual incidence of breast cancers associated with that fifteen-year E+P consumption was 12/1000 = 1.2%. Again, the data from the Collaborative Group Study is insufficient as a matter of law to put Wyeth on notice that breast cancer was a likely or probable

result from E+P consumption. (*See also* Response, Ex. 108, (Figure 9) (illustrating the marginal increase in the actual incidence of breast cancer associated with E+P consumption).)

Finally, the data in the 1998 Colditz study are likewise insufficient to create a genuine issue of material fact on Wyeth's knowledge. Though the study found that "existing evidence supports a causal relationship between use of estrogens and progestins, levels of endogenous estrogens and breast cancer incidence in post-menopausal women[,]" it did not produce data sufficient for a reasonable juror to find that breast cancer was a likely or probable result of Prempro consumption. (Response, Ex. 115, at 1.) Rather, the study found a relative risk of breast cancer of 1.35 for E+P consumption for five years or longer, which as explained above is insufficient, given the background risk and actual incidence of breast cancer in the general post-menopausal population, to create a factual dispute on likely or probable injury or Wyeth's knowledge of such. (Response, Ex. 115, at 4 (quoting the actual incidence data from the Collaborative Group Study (*see* Response, Ex. 108, at 11)).)

Notably, Mr. Scharff did not argue that these studies show that Wyeth should have known that the risk of breast cancer was likely or probable. Rather, he argued that "Wyeth learned of studies conducted by independent researchers in those years

that showed a real breast cancer risk with E+P." (Response 38.) The difference between a real, or "appreciable," risk of injury and a likely or probable risk of injury is one of the key differences between a negligence claim and a wantonness claim. *See* Part II.A (discussing that difference in Alabama law). Again, if the court were deciding summary judgment on the issue of Wyeth's knowledge of the risk of breast cancer under a negligence standard, the issue would be one for the jury. However, viewing these studies collectively and attributing complete knowledge of their results to Wyeth simply does not establish that Wyeth knew or should have known during the times relevant to this cause of action that breast cancer was a likely or probable event from its failure to adequately warn about the risks of breast cancer associated with Prempro.[30]

[30] Just as viewing these studies collectively does not create a genuine issue of material fact on Wyeth's knowledge of sufficient risk of breast cancer, viewing them in light of the universe of research on the risk of breast cancer available prior to the WHI study only heightens the lack of factual support for Mr. Scharff's wantonness claims. *See Torkie-Tork*, 739 F. Supp. 2d at 904 (Viewed in the light most favorable to the plaintiff, "23 of 43 pre-WHI studies did not show a statistically significant association between breast cancer in women who have ever used estrogen replacement therapy.").

Further, the court also notes that the aforementioned lack of genuine issues of material fact critical to Mr. Scharff's common law wantonness claims would apply equally to the "wantonness under AEMLD" claims the court previously found untimely. (Order 46-48.)

3. No Genuine Issue of Material Fact that the Prempro Breast Cancer Warning Was Inadequate

Mr. Scharff argues that he has produced evidence that Wyeth's breast cancer warnings were "watered down" and inaccurate and, thus, inadequate under Alabama law. (Response 23-25 (citing *Globetti v. Sandoz Pharm. Corp.*, No. CV-98-TMP-2649-S, 2001 U.S. Dist. Lexis 2093, at *34 (N.D. Ala. Feb. 2, 2001) (Putnam, M.J.)); *see also* Response 38-49.) Wyeth replies that there is no genuine issue of material fact on the adequacy of the Prempro breast cancer warning because: (1) it warned about breast cancer, the main harm suffered by Mrs. Scharff; and (2) it complied with FDA requirements for warning about the risk of breast cancer associated with Prempro.[31] (Reply 19-25.)

Under Alabama law, a *wanton* failure to warn claim focuses on whether the defendant "consciously and intentionally failed to give reasonable and adequate warnings with knowledge of, or reckless indifference to, the fact that the lack of warnings made [the plaintiff's] injury likely or probable." *Richards*, 21 F.3d at 1058.

[31] Wyeth's argument that its compliance with FDA requirements bars a jury question on a wanton failure to warn claim lacks merit. *See Richards*, 21 F.3d at 1059 (The defendant's "compliance with both federal regulations and industry practices is *some evidence* of due care.") (emphasis added); *Cessna Aircraft Co. v. Trzcinski*, 682 So. 2d 17, 22 (Ala. 1996) (finding that all of the wantonness evidence, including that Cessna's testing and inspection procedures which were approved by the FAA, was insufficient to support a jury verdict for punitive damages under the clear and convincing evidence standard).

"'[T]he existence of a duty to warn and the adequacy of a warning are questions of fact for the jury.'"[32] *Toole I*, 999 F.2d at 1433 (quoting *State Farm Fire & Casualty Co. v. J.B. Plastics*, 505 So. 2d 1223, 1227 (Ala. 1987)); *see also Deere & Co. v. Grose*, 586 So. 2d 196, 198 (Ala. 1991); *Globetti*, 2001 U.S. Dist. Lexis 2093, at *34. A jury may find a warning inadequate on a *negligent* failure to warn theory when the warning "understate[s] the risk" of injury suffered by the plaintiff. *Toole I*, 999 F.2d at 1433; *Globetti*, 2001 U.S. Dist. Lexis 2093, at *38. Moreover, "[u]nder the 'learned intermediary doctrine,' the adequacy of [Wyeth's] warning is measured by its effect on the *physician*, [Dr. Reiland], to whom [Wyeth] owed a duty to warn, and not by its effect on [Mrs. Scharff]." *Toole I*, 999 F.2d at 1433 (quoting *Stone v. Smith, Kline & French Lab.*, 447 So. 2d 1301, 1304-05 (Ala. 1984)).

However, "the issue of punitive damages [on a wanton failure to warn theory] should not go to the jury when a manufacturer took steps to warn plaintiff of the potential danger that injured him; those facts bar a finding that defendant was consciously indifferent." *Toole I*, 999 F.2d at 1436; *Richards*, 21 F.3d at 1059; *but see Globetti*, 2001 U.S. Dist. Lexis 2093 at *36-39 (relying on *Toole I*'s negligent failure to warn reasoning, but not discussing *Toole I*'s holding that the issue of

[32] The parties do not dispute that Wyeth had a duty to warn about the risk of breast cancer associated with the use of Preempro.

punitive damages on a wanton failure to warn claim cannot go to the jury where the defendant took steps to warn the plaintiff of the main harm she suffered and the way she came to suffer that harm).

Toole I prevents Mr. Scharff's wanton failure to warn claim from surviving summary judgment. It is undisputed that Wyeth warned Dr. Reiland that "[t]he effect of added progestins [to estrogen replacement therapy] on the risk of breast cancer is unknown, although a moderately increased risk [of breast cancer] in those taking combination estrogen/progestin therapy has been reported." (1998 PDR at 3121-22.) Further, Wyeth also warned,

> The effects of added progestin [to estrogen replacement therapy] on the risk of breast cancer are unknown. Some studies have reported a somewhat increased risk, *even higher than the possible risk associated with estrogens alone*. Others have not. Regular breast examinations by a health professional and monthly self-examination are recommended for all women.

(1998 PDR at 3124 (emphasis added).) Wyeth's Prempro label referenced the relative risk associated with estrogens alone, 1.3 to 2.0, which is a relative risk that actually exceeded that found for E+P in the WHI study (1.26). Wyeth warned Dr. Reiland that the risks of breast cancer associated with E+P consumption were unknown, but that some studies had reported a moderately increased risk, even greater than the relative risk associated with estrogens alone (1.3 to 2.0). The Prempro warning described the

main harm that Mrs. Scharff suffered, breast cancer; warned Dr. Reiland that there was a potential for a relative risk of breast cancer greater than 1.3 to 2.0; and forecast how she came to suffer that harm, consumption of combination estrogen/progestin therapy. Under *Toole I*, it may be that "[m]ore could have been done or said" by Wyeth, but on these facts, "[Wyeth] did not exhibit indifference toward safety."[33] 999 F.2d at 1436. Accordingly, Wyeth did not act wantonly as a matter of law, and, thus, summary judgment in Wyeth's favor is appropriate.[34]

In sum, and for the foregoing reasons in Part II.A, summary judgment is due to be granted in favor of Wyeth on Mr. Scharff's wanton failure to warn claim.

B. <u>Wanton Design Claim</u>

Wyeth argues that Mr. Scharff "has not provided any reasons why the Court should not grant summary judgment as to the [wanton defective design claim]." (Reply 43.) Wyeth is correct. Mr. Scharff has not argued that summary judgment is due to be denied on this claim, nor has he produced any evidence sufficient to create a genuine issue of material fact. Notably, Mr. Scharff did not produce evidence that

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[33] The reasoning for granting summary judgment for Wyeth on Mr. Scharff's common law wanton failure to warn claim would apply equally to his "wantonness under AEMLD" claim (failure to warn theory), which the court previously found untimely. (Order 46-48.)

[34] Again, if this were a *negligent* failure to warn claim, the evidence likely would present a question for the jury; however, Mr. Scharff's negligence claims are time-barred, as found by the court in its prior Order.

Wyeth "consciously and intentionally refused to employ available technology (some safer, practical, alternative design) in reckless disregard of the fact that its failure to do so made the risk of [breast cancer] probable or likely." *Richards*, 21 F.3d at 1058.

Accordingly, summary judgment is due to be granted on the wanton defective design claim, and the court need not address Wyeth's argument that Mr. Scharff cannot maintain a common law wanton defective design claim involving a prescription drug. (Reply 43-44.)

III. CONCLUSION

Based on the foregoing, and pursuant to Rule 56(f) of the Federal Rules of Civil Procedure, it is ORDERED that summary judgment is GRANTED for Defendants on Plaintiff's remaining wantonness claims. A separate judgment will be issued.

DONE this 19th day of September, 2011.

/s/ W. Keith Watkins
CHIEF UNITED STATES DISTRICT JUDGE