IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	**MDL No. 2:14-mn-02502-RMG** **CASE MANAGEMENT ORDER NO. 72** **This Order relates to all cases.**

This matter is before the Court on Pfizer's Motion to Exclude Expert Testimony and Claims that Lipitor is Not Effective for and Should Not Be Approved for Primary Prevention in Women, (Dkt. No. 970). For the reasons stated below, the motion is GRANTED IN PART AND DENIED IN PART.

I. Background

All Plaintiffs in this MDL are women who used Lipitor "to lower the LDL cholesterol and triglycerides in the blood and/or as a primary prevention measure to decrease the risk of developing CVD [cardio vascular disease]." (Dkt. No. 160 at ¶ 17). Plaintiffs generally allege that Lipitor caused their Type 2 diabetes and that Defendant failed to adequately warn them about the diabetes risk associated with Lipitor.[1] (*See generally* Dkt. No. 160). Plaintiffs also allege that Lipitor was negligently designed because, among other things, it "was not effective for women as a measure of primary prevention of CVD." (*Id.* at ¶ 80). Additionally, Plaintiffs allege claims based on the combination of alleged ineffectiveness and alleged dangerousness.

[1] Plaintiffs have primarily focused on their failure to warn claim. However, the Master Complaint alleges twelve causes of action including negligence, negligent misrepresentation, negligent design, and fraud and misrepresentation. (Dkt. No. 160).

(*See id.* at ¶ 67 (alleging that Defendant was negligent "[i]n its promotion of Lipitor (atorvastatin calcium) in an overly aggressive, deceitful and fraudulent manner despite the lack of evidence demonstrating its effectiveness in women and despite the evidence as to the product's defective and dangerous characteristics due to its propensity to cause Type 2 Diabetes."); *id.* at ¶ 80 (alleging the drug was negligently designed because "it contained insufficient, incorrect, and defective warnings," which failed to alert health care professionals and users "of the risks of adverse effects and the lack of benefit for women.")).

At issue in the instant motion are opinions by Plaintiffs' experts that (1) Lipitor is not effective for primary prevention in women, (2) that there is no evidence that Lipitor is effective for primary prevention in women, and/or (3) that Lipitor should not have been approved for primary prevention in women.[2] As an initial matter, Plaintiffs state in briefing that they "do not assert, and their experts do not opine that Lipitor is *not* effective for primary prevention in women. Rather, these experts opine that there is insufficient evidence to show that Lipitor *is* effective for primary prevention in women." (Dkt. No. 1046 at 6 (emphasis in original)). However, Plaintiffs do specifically allege in their Master Complaint that Lipitor is "***not effective*** for women as a measure of primary prevention of CVD," (Dkt. No. 160 at ¶ 80 (emphasis added)), and at least some of Plaintiffs' experts state this opinion. (*See* Dkt. No. 970-12 at 155-56 ("Q. Is it your opinion that women with diabetes receive no benefit from [] taking Lipitor? A. Correct.")). Therefore, where applicable, the Court will consider and address both opinions.

[2] Plaintiffs do not allege that Lipitor is ineffective in women for ***secondary*** prevention (i.e., for the prevention of CVD in women who have a history of coronary heart disease) and agree that it lowers cholesterol in women. (Dkt. No. 1046 at 6). In briefing, Plaintiffs define "primary prevention" as "preventing coronary heart disease in women with no prior history of such events." (Dkt. No. 1046 at 6).

Similarly, Plaintiffs state that they "do not allege that Lipitor . . . should never have been approved for use by women." (Dkt. No. 1046 at 33). While Plaintiffs have not alleged this in their Master Complaint, Dr. Abramson did state this opinion in his deposition. (*See* Dkt. No. 970-5 at 20 ("I would not have Lipitor be indicated for primary prevention in women."); *id.* at 20 ("Q. ...[Y]ou think that Lipitor prescriptions for women for primary prevention should be an off-label use. Is that right? A. Yes.")). Thus, the Court will address whether Dr. Abramson can testify to this at trial.

Pfizer argues that all of these opinions should be excluded under Fed. R. Evid. 702 and that Plaintiffs' lack of efficacy claims are preempted by federal law. (Dkt. No. 970). In particular, Plaintiffs claim that Defendant's labeling, advertising and promotion of Lipitor are misleading with regard to efficacy in women, and Defendant argues these particular claims are preempted by federal law. The Court will address the preemption issue first and then turn to Rule 702 and *Daubert*.

II. Preemption

A. Impossibility Preemption

"A fundamental principle of the Constitution is that Congress has the power to preempt state law." *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372 (2000). Even without an express statutory provision for preemption, the U.S. Supreme Court has held that state law is preempted by federal law when (1) Congress intends federal law to "occupy the field," or (2) where state law conflicts with a federal statute. *Id.* One variety of conflict preemption is "where it is impossible for a private party to comply with both state and federal law." *Id*; *see also id.* at 372 n.6; *Oneok, Inc. v. Learjet, Inc.*, 135 S. Ct. 1591, 1595 (2015); *Sprietsma v. Mercury Marine, a Div. of Brunswick Corp.*, 537 U.S. 51, 64 (2002). Defendant claims that impossibility

preemption is applicable here. In particular, Defendant claims that it could not have complied with any state law duty to change its label with regard to efficacy and still comply with its labeling requirement under federal law.[3] Thus, the Court must determine whether Defendant could change its label to indicate a "lack of benefit for women,"[4] as Plaintiffs argue Defendant had a duty to do under state law, and still comply with federal law.

B. FDA Approval Process

The Federal Drug and Cosmetic Act (FDCA) requires drug manufacturers to gain FDA approval before marketing or selling a drug in interstate commerce. 21 U.S.C. § 355(a). To gain FDA approval for a new drug, a manufacturer submits a new-drug application (NDA), and to gain approval for a new indication, a manufacturer submits a supplemental new-drug application (sNDA). *See* 21 C.F. R. § 314.1, *et. seq*. Among other things, such applications must include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b). Drug manufacturers must also submit proposed labeling, with annotations, to be used with the drug. 21 U.S.C. § 355(b)(1)(F); 21 C.F.R. § 314.50(c)(2)(i).

To approve a particular indication for use of a drug, the FDA must determine that there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof" and that "based on a fair evaluation of all material facts," the labeling of the drug is not "false or misleading in any particular." 21 U.S.C § 355 (d). "Substantial evidence" means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by

[3] The Court first addresses Plaintiffs' claims that Defendant should have changed Lipitor's label and then addresses claims based on the advertising and promotion of Lipitor.

[4] (Dkt. No. 160 at ¶ 80).

experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." *Id.* The FDA has discretion to determine "based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness." *Id.*

"The FDA's premarket approval of a new drug application includes the approval of the exact text in the proposed label." *Wyeth v. Levine*, 555 U.S. 555, 568 (2009) (citing 21 U.S.C. § 355; 21 C.F.R. § 314.105(b)). After FDA approval, the manufacturer may sell and distribute the drug without violating federal law as long as it uses the FDA-approved label. *In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 36 (1st Cir. 2015) (citing 21 U.S.C. §§ 331(c), 333(a), & 352(a), (c)).

C. Lipitor's Label

In 1996, the FDA approved Lipitor for reducing cholesterol. In 1998, the FDA approved its use by patients with elevated triglycerides, and in 1999, the FDA approved it to increase HDL. At issue in this motion is Lipitor's 2004 indication for use in the primary prevention of cardiovascular disease (CVD).[5] The 2004 indication on the label states:

> In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to:
> - Reduce the risk of myocardial infarction
> - Reduce the risk of stroke
> - Reduce the risk for revascularization procedures and angina.

(Dkt. No. 970-28 at 4). The FDA approved Lipitor for this indication based on the ASCOT clinical trial. The FDA approved the use generally, without indication as to gender. However,

[5] The FDA later approved other indications: for the reduction of heart attack and stroke in patients with type 2 diabetes but without coronary heart disease (CHD) and for secondary prevention in patients with CHD.

the FDA-approved label describing the ASCOT study stated that "[d]ue to the small number of events, results for women were inconclusive."[6] (Dkt. No. 970-28 at 18).

D. Changing the Label

There are two ways that a brand name drug manufacturer can change a drug's label that are pertinent here: (1) secure FDA approval or (2) make a change under the Changes Being Effected (CBE) regulations. 21 C.F.R. §§ 314.70(b), 314.70(c)(6)(iii); *see also In re Celexa*, 779 F.3d at 37. The U. S. Supreme Court has held that if a drug manufacturer must obtain FDA approval to take action to comply with state law, then the state law is preempted. *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2571 (2011) ("[W]hen a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency, that party cannot independently satisfy those state duties for pre-emption purposes."). Thus, the question becomes whether the Defendant could have corrected the alleged labeling deficiency without prior FDA approval by using the CBE regulation. *See In re Celexa*, 779 F.3d at 41 (stating that the U.S. Supreme Court had drawn a line "between changes that can be independently made using the CBE regulation and changes that require prior FDA approval"); *see also Wyeth v. Levine*, 555 U.S. at 568.

Under the CBE regulation, drug manufacturers may change a drug label, without prior FDA approval, "to reflect newly acquired information . . . to accomplish any of the following:

> (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

[6] The FDA later approved Lipitor for primary prevention in diabetic patients based on the CARDS study. (Dkt. No. 160 at 4, 18-19). The FDA-approved label states that in the CARDS study, "[a]n effect of LIPITOR was seen regardless of age, sex, or baseline lipid levels." (*Id.* at 19).

> (B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;
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> (C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;
>
> (D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or
>
> (E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

21 C.F.R. § 314.70(c)(6)(iii). Plaintiffs claim that Defendant should have changed Lipitor's label regarding efficacy under subsection (D) of this regulation.[7]

Applicable regulations also define "newly acquired information" for purposes of the CBE regulation:

> Newly acquired information means data, analyses, or other information ***not previously submitted to the agency***, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

21 C.F.R. § 314.3(b) (emphasis added). Thus, any claim that a drug label should be changed based on information previously submitted to the FDA is preempted because the CBE regulation cannot be used to make a label change based on such information. However, claims that a drug label should be changed based on "newly acquired information" not submitted to the FDA are not preempted by federal law. As the First Circuit explained:

> To the extent that the underlying policy issue is one of who decides whether and how a drug can be marketed, the line so drawn lets the FDA be the exclusive judge of safety and efficacy based on information available at the commencement of marketing, while allowing the states to reach contrary conclusions when new

[7] Plaintiffs also argue that Pfizer should have added warnings about the alleged risk of diabetes associated with Lipitor under subparagraph (A) of this regulation. Pfizer does not argue that these failure-to-warn claims are preempted by federal law.

> information not considered by the FDA develops. The CBE regulation, too, covers virtually all situations in which new information indicates new or greater risks, or misleading claims of efficacy. By hinging preemption on the availability of that procedure in a particular case, *Wyeth* effectively reserves the launch of new drugs to the expertise of the FDA, but then preserves a wide scope for the states in requiring manufacturers to respond to information not considered by the FDA.

In re Celexa., 779 F.3d at 41.

Here, the FDA approved the Lipitor label based on the ASCOT trial and data. It specifically approved the statement, based on ASCOT, that "[d]ue to the small number of events, results for women were inconclusive." (Dkt. No. 970-28 at 18). To the extent that Plaintiffs claim Lipitor's label should have included different statements about Lipitor's efficacy for primary prevention in women based on the ASCOT data, those claims are preempted. While Plaintiffs are correct that "new analyses of previously submitted data" are sufficient to invoke the CBE regulation, neither Plaintiffs nor their experts have identified any such "new analyses" of the ASCOT data that should have caused Defendant to change its label. The only "new analysis" of ASCOT efficacy data mentioned by Plaintiffs' experts is Dr. Wells' analysis, which was conducted as a part of this litigation.

The only "newly acquired information" mentioned by Plaintiffs in briefing is the CASHMERE study. (Dkt. No. 1046 at 32). Any claims that Defendant should have changed its label based on the CASHMERE study are not preempted, as the study would be "newly acquired information." Defendant argues that "the results of CASHMERE have no bearing on the primary prevention indications. . ." (Dkt. No. 1090 at 18). However, such arguments concern the sufficiency of evidence to survive summary judgment, not preemption. Thus, the Court does not address the argument here.

Finally, Plaintiffs argue that "new information about the increased risk of diabetes associated with statins generally, and Lipitor in particular, has continued to accumulate," that "[t]his accumulating information about diabetes and Lipitor has cast the lack of evidence of efficacy in a new light," and that "had Pfizer wished to change its label to make the lack of evidence of efficacy in this group clearer, it could have." (Dkt. No. 1046 at 32). The Court disagrees that new information regarding the risk of diabetes could serve a basis for a CBE label change regarding efficacy. As an initial matter, Pfizer has not claimed that Plaintiffs' failure to warn claims are preempted by federal law, and Plaintiffs are free to argue that "accumulating information about diabetes" should have caused Defendant to add or change warnings ***regarding diabetes***. However, Defendant could not, as Plaintiffs contend, "change its label to make the lack of evidence of efficacy in this group clearer," absent "newly acquired information" that "indications for use or claims for effectiveness" were "false, misleading, or unsupported." 21 C.F.R. §314.70(c)(6)(iii)(D). In other words, changes to statements regarding efficacy in the label must be based on newly acquired information regarding efficacy.

To hold otherwise would mean that ***any*** new information regarding a drug would allow a drug manufacturer, under the CBE regulation, to wholly re-write a drug label, completely divorced from the FDA-approved label, regardless of whether the new information was relevant to particular statements being changed or not. Such an interpretation is contrary to the regulatory scheme of the FDCA and contrary to the CBE regulation itself. Under the CBE regulation, a drug manufacturer can change a label "[t]o delete false, misleading, or unsupported indications for use or claims for effectiveness" when newly acquired information indicates, or "***reflect[s]***," that claims of effectiveness are "false, misleading, or unsupported." 21 C.F.R. §314.70(c)(6)(iii)

(emphasis added). Thus, under the CBE regulation, changes to statements regarding efficacy in the label must be based on newly acquired information regarding efficacy.

In sum, to the extent that Plaintiffs claim that a state law duty required Defendant to include different statements on Lipitor's label regarding Lipitor's efficacy for primary prevention in women, based on the ASCOT data or information solely related to the risk of diabetes, those claims are preempted.[8] To the extent that Plaintiffs claim that a state law duty required Defendant to include different statements on Lipitor's label regarding Lipitor's efficacy for primary prevention in women, based on CASHMERE or other newly acquired information, the claims are not preempted.

E. Advertising and Promotion Claims

Plaintiffs also claim that Defendant should have advertised or promoted Lipitor differently with regard to efficacy. Defendant contends such claims are also preempted.

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[8] An impossibility analysis usually compares specific state tort duties with federal labeling requirements. *See Mensing*, 131 S. Ct.at 2573. Indeed, in an individual case, a court may find that the plaintiff failed to state a claim under state law and, thus, moot the preemption issue. *See Strayhorn*, 737 F.3d at 395 (dismissing express-warranty claims because state law only allowed a cause of action where product labeling included a false statement and Plaintiffs only alleged the labeling was inadequate).

However, this MDL currently includes cases from 49 states, the District of Columbia, Puerto Rico, and the Virgin Islands. Analyzing specific tort duties in these 52 jurisdictions and then comparing them to federal labeling requirements would be onerous, and it is unnecessary. Tort law in particular jurisdictions may or may not require Defendant to change statements regarding efficacy in Lipitor's label, based on the ASCOT data. It is sufficient here to hold that, to the extent any state law does so require, Defendant cannot comply with that state law and federal labeling requirements simultaneously. *See, e.g., Schrock v. Wyeth, Inc.*, 727 F.3d 1273, 1286 (10th Cir. 2013) ("[S]tate tort law is preempted if it imposes a duty upon manufacturers to take some action that is prohibited under federal law."); *see also Drager v. PLIVA USA, Inc.*, 741 F.3d 470, 478 (4th Cir. 2014) (holding that "even if such claims are cognizable [under state law], they are preempted in the case of generic drug manufacturers.").

As an initial matter, any claims that Defendant should have simply stopped selling the drug to women for primary prevention is preempted. The U.S. Supreme Court has explicitly "reject[ed] this 'stop-selling' rationale as incompatible with [its] pre-emption jurisprudence," noting that such a rationale would render impossibility preemption "all but meaningless." *Mut. Pharm. Co. v. Bartlett*, 133 S. Ct. 2466, 2477 (2013). Plaintiffs appear to concede as much at oral argument and in post-oral argument briefing. (*See* Dkt. No. 1171 at 108 ("[T]hey don't have to stop selling the drug. I think that's what *Bartlett* said."); Dkt. No. 1282 at 4-5 ("A judgment grounded in state law that Pfizer's advertising contained untruths not found in the Lipitor label . . . [does not] require Pfizer to stop selling Lipitor, or even to stop selling it to women.").

The question remains whether state law claims based upon Defendant's promotion and advertising of Lipitor are preempted by the FDCA. The Court starts with the definition of "labeling," which is fairly broad. For purposes of the FDCA, the term "means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C § 321(m). The first clause of this definition "clearly embraces advertising or descriptive matter that goes with the package in which the articles are transported." *Kordel v. United States*, 335 U.S. 345, 349-50 (1948); *accord Strayhorn v. Wyeth Pharm., Inc.*, 737 F.3d 378, 394 (6th Cir. 2013). The second clause "plainly includes what is contained within the package whether or not it is 'upon' the article or its wrapper or container," but also includes any item that "supplements or explains" article regardless of whether it is physically attached to the package or container. *Id.* at 350; *accord Strayhorn*, 737 F.3d at 394.

Thus, labeling under Section 321(m) includes "[b]rochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion

picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the "Physicians Desk Reference") ***for use by medical practitioners, pharmacists, or nurses***, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor." 21 C.F.R. § 202.1(*l*)(2) (emphasis added). Furthermore, the U.S. Supreme Court has explicitly held that "Dear Doctor" letters also qualify as labeling for purposes of the FDCA. *Mensing*, 131 S. Ct. at 2576. "In essence, virtually all communication with medical professionals concerning a drug constitutes labeling." *Del Valle v. PLIVA, Inc.*, No. CIV.A. B:11-113, 2011 WL 7168620, at *4 (S.D. Tex. Dec. 21, 2011), *report and recommendation adopted sub nom. Del Valle v. Qualitest Pharm. Inc.*, No. CIV. B-11-113, 2012 WL 2899406 (S.D. Tex. June 22, 2012), *aff'd sub nom. Lashley v. Pfizer, Inc.*, 750 F.3d 470 (5th Cir. 2014). Thus, Plaintiffs' claims based on promotional material sent to medical professionals are preempted to the same extent as Plaintiffs' claims based on the Lipitor label are preempted. These materials are, in fact, part of Lipitor's labeling.

However, contrary to Defendant's argument, all of its advertising materials are not considered labeling. While promotional materials sent to medical professionals are explicitly defined as "labeling," other advertising is not. *See* 21 U.S.C. § 352(n) ("This paragraph (n) [regarding advertising] shall not be applicable to any printed matter which the Secretary determines to be labeling as defined in section 321(m) of this title."). Advertisements that are not considered labeling include "advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems." 21 C.F.R. § 202.1(*l*)(1). In other words,

advertising to the general public, as opposed to materials for use by medical professionals, is not considered labeling and, thus, can be changed without the need to invoke the CBE regulation. Defendant has not pointed to any authority stating that a brand name drug manufacturer cannot make any changes to its public advertising without changing the label.

To be sure, such advertising is still highly regulated by the federal government, *see* 21 C.F.R. § 202.1, and state law cannot require a manufacturer to take action with regard to its advertisements not allowed by federal law. However, Defendant has not pointed to any such conflict here. For example, Defendant notes that a manufacturer's advertisement "shall not recommend or suggest any use that is not in the labeling accepted" by the FDA. 21 C.F.R. § 202.1(e)(4). This restriction speaks only to uses ***not*** approved by the FDA. It does not apply here, where the use at issue ***has*** been approved by the FDA. Federal regulations also require that drug advertisements "present a true statement of information in brief summary relating to . . . effectiveness." 21 C.F.R. § 202.1(e)(1). However, Defendant has not argued that this requirement of federal law conflicts with the actions that Plaintiffs allege Defendant was required to take under state law.

Because Defendant has not shown a conflict between its alleged state law duties and federal law, the Court finds that Plaintiffs' state law claims based on Defendant's advertising to the general public are not preempted.[9]

[9] The Court makes this holding without prejudice to Defendant to raise preemption arguments based on specific state law requirements in individual cases.

III. Federal Rule of Evidence 702

A. Legal Standard

Under Rule 104(a) and 702, "the trial judge must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 589 (1993). Thus, the trial court must ensure that (1) "the testimony is the product of reliable principles and methods," that (2) "the expert has reliably applied the principles and methods to the facts of the case," and (3) that the "testimony is based on sufficient facts or data." Fed. R. Evid. 702(b), (c), (d). "This entails a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid," *Daubert,* 509 U.S. at 592-93, and whether the expert has "faithfully appl[ied] the methodology to facts." *Roche v. Lincoln Prop. Co.*, 175 F. App'x 597, 602 (4th Cir. 2006).

Factors to be considered include "whether a theory or technique . . . can be (and has been) tested," "whether the theory or technique has been subjected to peer review and publication," the "known or potential rate of error," the "existence and maintenance of standards controlling the technique's operation," and whether the theory or technique has garnered "general acceptance." *Daubert,* 509 U.S. at 593-94; *accord United States v. Hassan*, 742 F.3d 104, 130 (4th Cir. 2014). However, these factors are neither definitive nor exhaustive, *United States v. Fultz*, 591 F. App'x 226, 227 (4th Cir. 2015), *cert. denied*, 135 S. Ct. 2370 (2015), and "merely illustrate[] the types of factors that will bear on the inquiry." *Hassan*, 742 F.3d at 130. Courts have also considered whether the "expert developed his opinions expressly for the purposes of testifying," *Wehling v. Sandoz Pharm. Corp.*, 162 F.3d 1158 (4th Cir. 1998), or through "research they have conducted independent of the litigation," *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995) (on remand), and whether experts have "failed to meaningfully account for . . .

literature at odds with their testimony." *McEwen v. Baltimore Washington Med. Ctr. Inc.*, 404 F. App'x 789, 791-92 (4th Cir. 2010).

Rule 702 also requires courts "to verify that expert testimony is 'based on sufficient facts or data.'" *E.E.O.C. v. Freeman*, 778 F.3d 463, 472 (4th Cir. 2015) (quoting Fed. R. Evid. 702(b)). Thus, "trial judges may evaluate the data offered to support an expert's bottom-line opinions to determine if that data provides adequate support to mark the expert's testimony as reliable." *Id.* The court may exclude an opinion if "there is simply too great an analytical gap between the data and the opinion offered." *Id.* "The proponent of the [expert] testimony must establish its admissibility by a preponderance of proof." *Cooper v. Smith & Nephew, Inc.*, 259 F.3d 194, 199 (4th Cir. 2001).

The Court is mindful that the *Daubert* inquiry involves "two guiding, and sometimes competing, principles." *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 261 (4th Cir. 1999). "On the one hand . . . Rule 702 was intended to liberalize the introduction of relevant expert evidence," *id.*, and "the trial court's role as a gatekeeper is not intended to serve as a replacement for the adversary system." *United States v. Stanley*, 533 F. App'x 325, 327 (4th Cir. 2013), *cert. denied*, 134 S. Ct. 1002 (2014). On the other, "[b]ecause expert witnesses have the potential to be both powerful and quite misleading, it is crucial that the district court conduct a careful analysis into the reliability of the expert's proposed opinion." *United States v. Fultz*, 591 F. App'x 226, 227 (4th Cir. 2015), *cert. denied*, 135 S. Ct. 2370 (2015); *accord Westberry*, 178 F.3d at 261.

B. Dr. Wells Reanalysis of ASCOT Data

Dr. Wells is a statistician and was asked to "review statistical aspects of relevant scientific literature and data relating to the efficacy and outcome gender heterogeneity of various atorvastatin studies." (Dkt. No. 970-3 at ¶ 1).

1. Background

ASCOT-LLA tested Lipitor's efficacy in the primary prevention of coronary heart diseases (CHD) in patients with high blood pressure but normal blood lipids. (Dkt. No. 970-29 at 2). The Lipid Lowering Arm of the study included 10,305 patients, aged 40-79 years with at least three other cardiovascular risk factors but normal cholesterol and who had not experienced a cardiovascular event. (*Id.*). Participants were randomly assigned to a 10 mg dose of atorvastatin or placebo. (*Id.*). The study was stopped early, after a little over 3 years, because "atorvastatin had resulted in a highly significant reduction in the primary endpoint of CHD events compared with placebo and a significant reduction in the incidence of stroke." (*Id.* at 4). This study was the basis of the FDA's approval of Lipitor for primary prevention.

Because one of the risk factors that allowed participants into the study was "male sex," only 1,942 of the 10,305 participants were women. (*Id.* at 8, Table 4). While the study showed benefits overall, "no benefit was apparent among [the subgroup] of women." (*Id.* at 6). Nineteen (19) women on Lipitor and 17 women on placebo experienced a primary endpoint event defined as "non-fatal myocardial infarction and fatal coronary heart disease." (*Id.* at 8, Table 4). The authors hypothesized "[t]he apparent lack of significant benefit of atorvastatin on the primary endpoint among women may reflect the small number of events they experienced (36 occurrences of the primary endpoint)." (*Id.* at 8). As to the secondary endpoint of total

cardiovascular events and total coronary events, women on Lipitor did have a lower rate of these events, but the difference was not statistically significant. (*Id.* at 6)

While there was no apparent benefit looking at only at the data for women, the authors also tested for gender heterogeneity and found none. Statistical tests of heterogeneity are used to assess whether the observed difference in results for a particular subgroup is greater than expected to occur by chance. If there is statistically significant heterogeneity for a particular subgroup, researchers do not infer that the overall results of the study apply to that particular subgroup. The ASCOT authors found "no significant interaction between sex and the impact of statin on the primary endpoint." (*Id.* at 6). In other words, authors did not find any heterogeneity; there was no apparent difference in treatment effect based on gender. (*Id.*).

Dr. Wells conducted his own analysis and opines that, "[t]here is significant gender heterogeneity in the ASCOT trial for all endpoints. In other words, the effectiveness of treatment varied by gender." (Dkt. No. 970-3 at ¶ 3). Dr. Wells reached a conclusion different from the study authors because he used a different statistical test. The ASCOT study pre-specified the Cox proportional hazards model, the most commonly used test, to be used to determine heterogeneity. (Dkt. No. 970-14 at 152-53). Dr. Wells used a difference statistical test called the Aalen's linear hazards model.

Dr. Wells opines that the Cox proportional hazards model is not appropriate for use with the ASCOT data. The Cox proportional hazards model assumes that the hazard ratio is constant over time. (Dkt. No. 970-3 at ¶ 7). The Aalen's linear hazards model assumes the ratio varies over time. (*Id.* at ¶ 8). There are statistical tests that can be run on data sets to determine if the assumptions of the Cox model are true for a particular data set. Dr. Wells ran one of these tests and found that the assumption is not true for the ASCOT data, and therefore opined that the Cox

test is not valid. (*Id.* at ¶ 9). Thus, he applied the Aalen model, and this model showed a significant difference between men and women, indicating that "it is inappropriate to infer that the outcomes for women are similar to the outcomes for men or for the combined population." (*Id.* at ¶ 10).

Pfizer argues that the Cox proportional hazards model is the "generally accepted method" for testing for heterogeneity whereas the Aalen model is "an obscure statistical model" that is not used "in this context" and that Dr. Wells' analysis reanalysis is "litigation-driven" and should be excluded. (Dkt. No. 1090 at 7, 13).

2. Discussion

The Court finds Dr. Wells' reanalysis admissible under Rule 702. This Court has previously held in this MDL that "courts are appropriately skeptical of *post-hoc*, reanalyses conducted solely for the purpose of litigation that reach conclusions contrary to peer-reviewed published studies." (CMO 67, Dkt. No. 1412 at 11). However, as the Court stated in CMO 54, "[t]his is not to say that a reanalysis of published data is never admissible." (CMO 54, Dkt. No. 1258 at 32; *accord* CMO 67, Dkt. No. 1412 at 11). Instead, the expert must provide an explanation for why a reanalysis is warranted, or in the words of the Ninth Circuit, he must "validate" his reanalysis in some way. (*Id.*); *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1320 (9th Cir. 1995). Dr. Wells has provided such an explanation.

Dr. Wells ran a statistical test used for determining whether the underlying assumption of the Cox proportional hazards model is valid for a particular data set, and he found that the assumption was not valid for the ASCOT data set. (Dkt. No. 970-3 at ¶ 9). Because he found the assumption of the Cox model violated, Dr. Wells turned to a different statistical test, the Aalen model. When asked why others did not also use the Aalen model, Dr. Wells testified that

"I think I was the only one to ever check the proportional hazards assumption." (Dkt. No. 970-14 at 154). This is a valid reason for conducting a reanalysis. The Aalen model is not one made up by Dr. Wells in this litigation but is one that has been tested and subjected to peer review. While Defendant is correct that the Cox model is more commonly used, the Aalen model is an alternative recognized in peer-reviewed literature. (Dkt. No. 970-3 at 7 n.2). Defendant appears to admit that the Aalen model is "generally accepted" but implies that Dr. Wells has not "establish[ed] an adequate scientific foundation for using it." (Dkt. No. 1090 at 14-15). However, he has done just that by finding the underlying assumption of the Cox model violated. Therefore, the Court denies Defendant's motion to exclude Dr. Wells' reanalysis of the ASCOT data under Rule 702.

C. Primary Prevention Efficacy Studies

Plaintiffs' experts opine that there is no evidence to support the statement that statins are effective for primary prevention in women.[10] (*See, e.g.*, Dkt. No. 970-3 at ¶¶ 4-5). Thus, it is helpful to review the published studies on this topic before evaluating the experts' opinions.

1. JUPITER

The JUPITER (2008) study[11] included 17,802 apparently healthy men and women with normal LDL levels but high-sensitivity C-reactive protein levels. (Dkt. No. 970-44 at 2). Participants were from 1,315 sites in 26 countries. (*Id.* at 3). Participants were randomly assigned to 20 mg of rosuvastatin (Crestor) or a placebo. (*Id.* at 2). The study was stopped early

[10] Plaintiffs do not allege that Lipitor is ineffective in women for ***secondary*** prevention (i.e., for the prevention of CVD in women who have a history of coronary heart disease), but that it is ineffective (or that there is no evidence to demonstrate its effectiveness) for primary prevention (i.e., the prevention of CVD in women who do not have a history of coronary heart disease). (Dkt. No. 1046 at 6).

[11] JUPITER stands for Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin.

because of the CVD benefits of the rosuvastatin. Of the 17,802 participants, 6,801 (38.2%) were women. (*Id.* at 6). The authors found no evidence of heterogeneity among subgroups. (*Id.* at 7). "Relative hazard reductions in the rosuvastatin group were similar for women (46%) and men (42%) and were observed in every subgroup evaluated." (*Id.*). ***The reduction in risk was statistically significant for women***. (*See id.* at 10, Figure 2 (showing a confidence interval completely below 1 for women)).

In a separate sex-specific analysis of JUPITER, study authors found a hazard ratio of .54, with a 95% confidence interval of .37 to .8, (p=002), for women with regard to any primary endpoint. (Dkt. No. 970-45 at 4). This is statistically significant and similar to the hazard ratio for men, which was .58 with a confidence interval of .45 to .73. (*Id.*). There was also no heterogeneity. (*Id.* at 5).

2. CARDS

CARDS[12] (2004) tested the efficacy of Lipitor for primary prevention of major cardiovascular events in patients with type 2 diabetes but normal LDL levels. (Dkt. No. 970-42 at 2). The study included 2,838 patients aged 40-75 with type 2 diabetes, no history of cardiovascular disease, an LDL of 4.14 mmol/L or less, a fasting triglyceride of 6.78 mmol/L or less and at least one of the following: retinopathy, abluminuria, current smoking, or hypertension. (*Id.*). Participants were randomly assigned to 10 mg of atorvastatin or placebo. The study was terminated 2 years early because of the benefits of Lipitor. (*Id.*). Thirty-two percent (32%) of the participants were women. (*Id.* at 5, Table 1). "Allocation to atorvastatin was associated with at 37% reduction in the incidence of major cardiovascular events (p=.001)." (*Id.* at 7). "Adjustment for baseline age and sex . . . made no difference to the estimate of the

[12] CARDS stands for Collaborative Atorvastatin Diabetes Study.

treatment effect (36% risk reduction, p=0.002)." (*Id.* at 7-8). "Prespecified tests for evidence of heterogeneity of effect were not significant for sex (p=0.59)." (*Id.* at 8).

3. Mora (2010)

Mora (2010) conducted several meta-analyses of statin therapy for the primary prevention of CVD in women. (Dkt. No. 970-45 at 3). The authors first ran the statistical tests looking only at trials that were "exclusively" primary prevention trials, AFCAPS/TexCAPS, MEGA, and JUPITER. (*Id.* at 3, 6). They found that "[c]ompared to placebo, statin therapy in women significantly reduced CVD by about one-third." (*Id.* at 6). The relative risk ratio for women was .63, with a confidence interval of .49 to .82, p<.001. (*Id.*) There was no gender heterogeneity. (*Id.*).

The study authors then ran the analysis again with 5 trials, the three above plus two "predominately" primary prevention trials, ASCOT and ALLHAT-LLT. (*Id.* at 3, 6-7). The results were similar but not statistically significant. The relative risk was .79 with a 95% confidence interval of .59 to 1.05, p=.1. (*Id.* at 6-7). However, there was no statistically significant gender heterogeneity. (*Id.* at 7).

The study authors then ran the analysis again with 7 trials, the 5 above plus two that "included a substantial number of women without known CVD." (*Id.* at 3). These trials were HPS and PROSPER. (*Id.*). In this analysis, the results became statistically significant again, with a relative risk of .82 and a confidence interval of .69 to .98, p=.03. (*Id.* at 7). The study authors concluded that their results "suggest[] that the prior lack of significance may have been due to the inadequate number of events among women in these studies." (*Id.* at 8).

4. Kostis (2012)

Kostis (2012) reached similar results. The express purpose of this study was to evaluate the effect of statins in decreasing cardiovascular events in women versus men. (Dkt. No. 970-46 at 2). The authors identified and considered data from 18 randomized clinical trials of statins with sex-specific outcomes. (*Id.*). The study found that "[t]he benefit of statins was statistically significant in both sexes, regardless of the type of control, baseline risk, or type of endpoint and in both primary and secondary prevention." (*Id.* at 2). The Odds Ratio for women, overall all 18 studies, was .81 with a confidence interval of .75 to .89, p<.0001. (*Id.*). The Odds Ratio for men was .77 with a confidence interval of .71 to .83, p<.0001. (*Id.*).

Analyses were also done separately for studies aimed at primary and secondary prevention. The authors found that "[i]n women, the benefit with respect to the primary event seemed more pronounced in secondary prevention trials than in primary prevention trials," but both were statistically significant. (*Id.* at 6). For primary prevention, the odds ratio was .85 with a confidence interval of .75 to .98. (*Id.*). For secondary prevention the odds ratio was .78, with a confidence interval of .70 to .88. (*Id.*).

The all-cause mortality rate was also lower for women in the statin groups both when all 18 studies were considered together (odds ratio of .9, with a confidence interval of .82 to .99) and when only the primary prevention studies were considered (odd ratio of .87, with a confidence interval of .78 to .97).

Because "the distinction between primary and secondary prevention is ambiguous," the authors also "performed analyses by risk level." (*Id.* at 8). "Meta-analysis by level of risk indicated a statistically significant benefit of statin therapy at all levels of risk in . . . women." (*Id.* at 6). Lower-risk women actually saw greater benefit. For high risk, the odds ratio was .88

with a confidence interval of .81 to .95. For medium risk, the odds ratio was .75 with a confidence interval of .64 to .89. For low risk, the odds ratio was .59 with a confidence interval of .41 to .87. (*Id.*).

5. CTT Collaboration (2015)

Another study of note is the 2015 meta-analysis by the CTT Collaboration. This was a meta-analysis conducted specifically to "compare the effects of statin therapy between women and men." (Dkt. No. 970-48 at 2). Instead of dividing studies by the primary/secondary distinction, the authors considered and controlled for cardiovascular risk across all studies. The authors looked at 27 trials, 22 trials with statin versus control and 5 with high-dose versus lose-dose statins. The authors used 99% confidence intervals instead of 95% confidence intervals. (*Id.*). According to the authors, this study is the "largest meta-analysis to date comparing statin efficacy by sex, and it is the only such analysis to adjust in detail for cardiovascular risk." (*Id.* at 7).

The main finding of the study is that women had a lower baseline risk for cardiovascular disease, but that, "[i]n men and women at an equivalent risk of cardiovascular disease, statin therapy is of similar effectiveness for the prevention of major vascular events." (*Id.*). The authors first looked at the reduction in LDL levels in men and women, and then looked at, for every 1.0 mmol/L reduction in LDL, what was the corresponding reduction in major vascular events. (*Id*). The authors found that, overall in the 27 trials, for every 1 mmol/L reduction in LDL, there was a 21% reduction of major vascular events, with significant reductions in both men and women. (*Id.* at 5). After adjusting for "non-sex differences in baseline prognostic characteristics," i.e., risk factors, there was no difference between proportional effects of statins in women and men. (*Id.*).

Looking at only the 22 trials that compared statins to a placebo, "the proportional reductions in major vascular events per 1 mmol/L reduction in LDL cholesterol seemed slightly smaller in women than in men . . . but they were highly significant ($p<.0001$) in both women . . . and men." (*Id.* at 6). The authors found similar results for specific types of cardiovascular events. (*Id.* at 6-7). When authors adjusted for baseline risk factors, any difference between the sexes generally disappeared. (*Id*).

The authors stated that "we have been able to demonstrate conclusively that among women and men at similar risk of major vascular events, the proportional and absolute effects of statin therapy on major vascular events and mortality were similar." (*Id.* at 7). "This is true . . . when statin therapy was used for the primary prevention of major vascular events in low-risk populations." (*Id.*).

D. Dr. Wells

Dr. Wells opines that "[t]here is no statistically significant evidence to support the claim that statins provide primary cardioprotection for women," that "[n]o proper meta-analysis of RCTs provides statistically significant evidence of primary CV prevention for women," and that "[n]on-reporting of RCTs and the improper pooling of trials for meta-analyses has contributed to the misperception that there is RCT evidence proving statins provide primary prevention in women." (Dkt. No. 970-3 at ¶¶ 4-5). Importantly, Dr. Wells does not opine that some studies show benefits and others do not (i.e., that there is conflicting evidence), and he does attempt to resolve conflicts to reach the opinion that it is unlikely that statins are useful for primary prevention in women. Rather, Dr. Wells opines that there is ***no*** evidence—none—supporting the use of statins for primary prevention in women. For such an opinion to be reliable and admissible under Rule 702, Dr. Wells must have considered all relevant evidence and there must

actually be no statistically significant evidence supporting the use of statins for primary prevention in women. One study providing such evidence makes his statement that there is "no" such evidence false and unreliable. As explained above, there is at least one such study.

JUPITER provides statistically significant evidence that statins have primary prevention benefits for women. Dr. Wells notes that JUPITER's results are "exceptional[]" and opines that certain meta-analyses finding primary prevention benefits in women would not reach statistically significant findings if JUPITER were not included. (Dkt. No. 970-3 at ¶ 29). However, Dr. Wells never contests JUPITER as a primary prevention study or that it found a statistically significant benefit for women. (*See* Dkt. No. 970-3). Thus, it is simply false to say there is no such evidence.

Dr. Wells also does not challenge the findings of CARDS. Indeed, he readily admits them. (Dkt. No. 970-14 at 115-16). However, he disregards CARDS because he says that diabetes is a "risk equivalent" to coronary heart disease (CHD). In his deposition, Dr. Wells explains that the data show that statins provide cardiovascular benefits to women if they have had a prior coronary event (secondary prevention) ***or*** if they have a "risk equivalent." (Dkt. No. 970-14 at 80, 137-38). He states that diabetes is a "risk equivalent" or a "risk factor," so there is a benefit from the drug for diabetic women. He admits that CARDS shows a benefit for women and admits that CARDS is "primary prevention at one level," but disregards the findings as not meaningful because diabetes is a "risk equivalent" for CHD. (Dkt. No. 970-14 at 85, 115-16). Dr. Wells also admits that other women who have not had prior coronary events would benefit from statins based on risk factors but he doesn't "know the details" or "the level of end cutoffs." (Dkt. No. 970-14 at 113). In other words, Dr. Wells believes that other women with "risk equivalents" of CHD would benefit from statins in a primary prevention context, but he does not

seem to know what these "risk equivalents" are. For instance, he does not know "the levels or risk factors, for LDL," and, thus, he does not know whether a woman with elevated LDL with no prior cardiovascular events would receive a benefit from statins. (*Id.*). At least when discussing CARDS, Dr. Wells' opinion is based on a participant's level of risk, ***not*** whether the study is technically a primary prevention and secondary prevention study.[13]

This stands in contrast to his opinion regarding the CTT Collaboration study. Dr. Wells states that the CTT study "improperly combine[s] primary and secondary prevention RCT results." (Dkt. No. 970-3 at ¶ 27). The study does combine both types of studies but adjusts for cardiovascular risk "in detail." When discussing CARDS or JUPITER, which are primary prevention studies that directly contradict Dr. Wells' "no evidence" opinion, Dr. Wells believes it is important to consider the risk of the participants, rather than simply whether the study is technically a primary prevention or secondary prevention study. (*See, e.g.*, Dkt. No. 970-14 at 138-39). However, when a study specifically considers risk, rather than the simple distinction between primary and secondary studies, Dr. Wells disregards it as improperly combining the two types of studies. He cannot have it both ways and produce a reliable opinion under Rule 702. *See, e.g., In re Rezulin Products Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004) ("[The expert's] selectivity in defining the universe of relevant evidence thus violated his own standard of proper methodology.").

Dr. Wells's main critique of the Mora meta-analysis is that it included JUPITER, which he considers to be an outlier. (Dkt. No. 970-3 at ¶ 29). However, JUPITER itself is evidence in support of the use of statins in primary prevention for women.

[13] In briefing, Plaintiffs define "primary prevention" as "preventing coronary heart disease in women with no prior history of such events." (Dkt. No. 1046 at 6).

In short, there ***is*** statistically significant evidence that statins are effective for primary prevention in women. Both JUPITER and CARDS constitute such evidence, as does the Mora meta-analysis. Dr. Wells admits that both JUPITER and CARDS are primary prevention studies and that they showed effectiveness in women. While Dr. Wells wishes to disregard CARDS because diabetes is a "risk equivalent" of CHD, his efficacy opinion was not caveated by "risk equivalents," the presence of particular risk factors, or a narrow definition of primary prevention. Regardless, even without CARDS, JUPITER provides statistically significant evidence on the issue, as does Mora.

Rule 702 also requires courts "to verify that expert testimony is 'based on sufficient facts or data.'" *E.E.O.C. v. Freeman*, 778 F.3d 463, 472 (4th Cir. 2015) (quoting Fed. R. Evid. 702(b)). Thus, "trial judges may evaluate the data offered to support an expert's bottom-line opinions to determine if that data provides adequate support to mark the expert's testimony as reliable." *Id.* The court may exclude an opinion if "there is simply too great an analytical gap between the data and the opinion offered." *Id.* Here, the Court finds that there is simply "too great an analytical gap" between the data and Dr. Wells' "no evidence" opinion. Therefore, the Court excludes it under Rule 702.[14]

E. Dr. Roberts

Dr. Roberts opines that "[t]here is no convincing evidence that Lipitor is effective for primary prevention of heart disease in women." (Dkt. No. 970-2 at 5). She also opines that "[n]ot only has Lipitor not been shown to reduce hard endpoints like heart attack, CVD death or

[14] Dr. Wells also opines that Pfizer's label, which states that the "results for women were inconclusive" based on the ASCOT trial is "misleading." (Dkt. No. 970-3 at ¶ 41). As explained above, such a claim is preempted by the FDCA. Thus, this opinion is excluded under Fed. R. Evid. 402 and 403.

stroke when used for primary prevention, no other statin has been shown to do so either." (*Id.* at 7).

With regard to her Lipitor opinion, Dr. Roberts discusses ASCOT and CARDS. (*Id.* at 5-6, 8). However, Dr. Roberts adamantly refuses to consider the evidence from CARDS that the observed benefits are applicable to women.[15] She simply will not discuss it. (Dkt. No. 970-12. at 152-56). She notes that when looking only at the data for the subgroup of women, the reduction in cardiovascular events was not statistically significant. (*Id.*; Dkt. No. 970-2 at 8). While a fine observation, it says very little. The study was not designed and powered to detect a difference in risk in the women-only subgroup, and the lack of significance could be simply due to the lack of power or due to the fact that no actual reduction occurred. (*See* Dkt. No. 1440-5 at 190 (discussing implications of non-statistically significant results)). However, there are statistical tests to determine whether the observed results for particular subgroups, like women, are meaningfully different from the results overall. These tests are referred to as tests of heterogeneity, and when there is no significant gender heterogeneity, it is appropriate to infer that the outcomes for women are similar to the outcomes for the combined population. (*See* Dkt. No. 970-3 at ¶¶ 6-10; *see also id.* at ¶ 10 (finding that when there ***is*** significant gender heterogeneity, "it is inappropriate to infer that the outcomes for women are similar to the outcomes for men or for the combined population.")).

In CARDS, "[p]respecified tests for evidence of heterogeneity of effect were not significant for sex (p=0.59)." (Dkt. No. 970-42 at 8). Furthermore, "[a]djustment for baseline age and sex . . . made no difference to the estimate of the treatment effect (36% risk reduction,

[15] Dr. Roberts appears to consider CARDS to be a primary prevention study. (Dkt. No. 970-12 at 152 ("I think that we can say from the CARDS trial that Lipitor for primary prevention in diabetic women in that study did not show a significant benefit.")).

p=0.002)." (*Id.* at 7-8). Tellingly, Plaintiffs statistician Dr. Wells, who understands the concept of statistical heterogeneity, readily admits that CARDS shows beneficial effects for women, (Dkt. No. 970-14 at 137-38), and the FDA-approved label states that, in the CARDS study, "[a]n effect of LIPITOR was seen regardless of age, sex, or baseline lipid levels." (Dkt. No. 160 at 19). However, Dr. Roberts will not discuss this statistical evidence that the CARDS findings are applicable to women.

Failing to adequately account for contrary evidence is not reliable or scientifically sound. *See McEwen v. Baltimore Washington Med. Ctr. Inc.*, 404 F. App'x 789, 791-92 (4th Cir. 2010) (upholding exclusion of expert testimony where experts "failed to meaningfully account for . . . literature at odds with their testimony"); In *re Zoloft (Sertraline Hydrochloride) Products Liab. Litig.*, 26 F. Supp. 3d 449, 460-61 (E.D. Pa. 2014) ("The Court finds that the expert report prepared by Dr. Bérard does selectively discuss studies most supportive of her conclusions . . . and fails to account adequately for contrary evidence, and that this methodology is not reliable or scientifically sound."), *reconsideration denied*, No. 12-MD-2342, 2015 WL 314149 (E.D. Pa. Jan. 23, 2015). It is especially egregious here, where Dr. Roberts opines that there is ***no*** evidence indicating that Lipitor is effective for primary prevention in women and simply refuses to discuss or account for the statistical evidence that indicates such a benefit.

With regard to Dr. Roberts' opinion on the efficacy of statins generally, she has failed to consider important evidence contrary to her opinion. She briefly discusses JUPITER and AFCAPS/TexCAPS,[16] (Dkt. No. 970-2 at 7-8), but she does not mention any of the meta-

[16] Dr. Roberts argues that JUPITER's consideration of "'softer' endpoints," such as revascularization and angina, is "specious." (Dkt. No. 970-2 at 7). It is worth noting that the 2004 indication specifically indicates the use of Lipitor to "[r]educe the risk for revascularization procedures and angina." (Dkt. No. 970-28 at 4).

analyses discussed above that are contrary to her opinion.[17] Again, her failure to consider contrary evidence is especially egregious given her opinion that ***no*** such evidence exists. Her failure to account for these meta-analyses, ***all*** of which contradict her conclusion, renders her opinion unreliable.[18] *In re Rezulin Products Liab. Litig.*, 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005) ("[I]f the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable."); *see also In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007) ("He reaches his opinion by . . . cherry-picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion. Dr. Doherty's opinion does not reflect scientific knowledge, is not derived by the scientific method, and is not 'good science.'"). Therefore, the Court excludes Dr. Roberts's efficacy opinions under Rule 702.

F. Dr. Quon

Dr. Quon opines that "[t]here is no convincing evidence that there is a clinical benefit for women using Lipitor for primary prevention."[19] (Dkt. No. 972-42 at 38). Dr. Quon reaches this

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[17] Dr. Roberts lists these meta-analyses at the end of her report in an appendix of "Materials Considered and Relied Upon." (Dkt. No. 970-2 at 45-53). However, she does not mention them in her report or account for them in anyway.

[18] To the extent that Dr. Roberts opines Lipitor and/or statins are ineffective for primary prevention in women, these opinions are excluded for the same reasons. (*See* Dkt. No. 970-12 at 155-56 ("Q. Is it your opinion that women with diabetes receive no benefit from [] taking Lipitor? A. Correct.")).

[19] Dr. Quon was not specifically mentioned in Defendant's original written motion. (Dkt. No. 970). However, Dr. Quon makes the same "no evidence" opinion as was addressed by the motion, the Court understood his opinion to be covered by the motion, the parties presented argument on his opinion at the hearing on Defendant's motion, and Plaintiffs were allowed to submit supplemental briefing regarding Dr. Quon after the hearing on the motion. (*See* Dkt. No.

conclusion with less than a page-and-a-half of analysis, focused on cherry-picked data. (*Id.* at 38-39). He discusses ASCOT, CASHMERE and Mora. (*Id.*). However, he fails to mention or consider JUPITER, CARDS, Kostis, o r the CTT Collaboration study. (*See id.*).

Even more indicative of his cherry-picking is Dr. Quon's discussion of Mora. As explained above, Mora conducted three separate meta-analyses, including studies that were "exclusively" primary preventions studies, studies that were "predominately" primary prevention studies, and studies that "included a substantial number of women without known CVD," respectively. (Dkt. No. 970-45 at 3). Two of these three meta-analyses found statistically significant results in the reduction of cardiovascular events for women. (*See* Dkt. No. 970-45). However, Dr. Quon chose to discuss only one of these three meta-analyses, the one without statistically significant results, and represented this one meta-analysis as the entirety of the study, stating, "[i]n their analyses, compared with placebo, statin therapy was not significantly associated with a reduction in total CVD." (Dkt. No. 972-42 at 38).

Basing an opinion on such cherry-picked data is unreliable and does not satisfy *Daubert*. *See Barber v. United Airlines, Inc.*, 17 F. App'x 433, 437 (7th Cir. 2001) ("Because in formulating his opinion Dr. Hynes cherry-picked the facts he considered to render an expert opinion, the district court correctly barred his testimony because such a selective use of facts fails to satisfy the scientific method and *Daubert*."); *Fail-Safe, L.L.C. v. A.O. Smith Corp.*, 744 F. Supp. 2d 870, 889 (E.D. Wis. 2010) ("[I]t is readily apparent that Dr. Keegan all but 'cherry picked' the data he wanted to use, providing the court with another strong reason to conclude that the witness utilized an unreliable methodology."); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007) (excluding expert

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1171 at 105-06, 125-26; Dkt. No. 1159 at 35-36). Thus, the Court will address the motion with regard to Dr. Quon as well.

testimony where expert "reaches his opinion by first identifying his conclusion . . . and then cherry-picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion"). As with Dr. Roberts, Dr. Quon's failure to consider contrary evidence is especially egregious given his opinion that ***no*** such evidence exists. Therefore, Dr. Quon's opinion that "[t]here is no convincing evidence that there is a clinical benefit for women using Lipitor for primary prevention" is excluded under Rule 702.

G. Dr. Fleming

Unlike other experts, Dr. Fleming does not offer an opinion on whether there is evidence to support the claim that Lipitor and/or statins are effective for primary prevention in women. (*See* Dkt. No. 970-6 at 228-29). Rather he opines that "the ASCOT data did not establish efficacy of Lipitor in women for primary prevention, and the label was misleading on this point." (Dkt. No. 970-4 at 35; s*ee also id.* at 39 ("The label was . . . misleading with respect to efficacy in women."). As explained above, any claims that the Lipitor label was misleading based on ASCOT are pre-empted. Therefore, this testimony is irrelevant. To the extent that it has any marginal relevance, it would be confusing and misleading to the jury to hear testimony on the allegedly misleading nature of the Lipitor label's description of ASCOT when such allegations cannot be the basis of Plaintiffs' claims. Therefore, this testimony is excluded under Fed. R. Evid. 402 and 403.

H. Dr. Abramson

Section VI of Dr. Abramson's report is titled "Lack of Evidence That Lipitor Provides Benefit In Primary Prevention Women." (Dkt. No. 970-1 at 70). In this section of his report, he opines that

- "The ASCOT trial did not . . . demonstrate a benefit in women";

- "[R]elevant cholesterol treatment guidelines (and the sources upon which they rely) did not, and do not, establish evidence that Lipitor provides a benefit in primary prevention women";

- "The CTT meta-analyses based on patient-level efficacy data, do not provide evidence that cholesterol-lowering statin drugs provide benefit to primary prevention women"; and

- "[R]elevant guidelines for the primary prevention of cardiovascular disease did not, and do not, contain evidence that Lipitor reduces the incidence of CVD in women without pre-existing heart disease or CHD risk-equivalent conditions."

(*Id.* at 70, 88, 102, 112). These opinions all concern particular pieces of evidence. In his report, Dr. Abramson does not purport to undertake a comprehensive literature review and make the sweeping opinion that there is no evidence whatsoever to support the use of statins for primary prevention in women. However, he does state such an opinion in deposition. (*See* Dkt. No. 974-1 at 20 ("[T]he evidence that exists does not show a benefit for primary prevention in women."), 47 ("I have not seen clinical trial evidence that shows that there's a primary prevention benefit in women."), 238 ("I think that there is no[] evidence to support the efficacy of statins for women in primary prevention.")).

Because this opinion is not specifically stated in his report, it is not clear if Plaintiffs intend for Dr. Abramson to offer this opinion at trial. However, because he repeatedly states this opinion in deposition, the Court will address it. As with Plaintiffs' other experts, Dr. Abramson cannot offer an opinion that "there is ***no*** evidence" to support the efficacy of statins for primary prevention in women, if he has failed to consider and address all evidence that purports to support such efficacy claims. Here, Dr. Abramson has not discussed or addressed the Mora meta-analyses[20] or the Kostis study in his report. Because he has not addressed these studies,

[20] Dr. Abramson did mention Mora's analysis of gender specific data from JUPITER, but not Mora's meta-analyses. (Dkt. No. 974-2 at ¶ 269). Dr. Abramson's only critique of JUPITER was that it included "soft" endpoints like revasularization as well has "hard" endpoints like heart attack and stroke. Again, it is worth noting that the 2004 indication specifically indicates the use

which are published in peer-reviewed journals and which explicitly state they support the efficacy of statins for primary prevention in women, Dr. Abramson's opinion that no such evidence exists is unreliable. *In re Rezulin*, 369 F. Supp. 2d at 425 ("[I]f the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable."); *In re Zoloft* ("The Court finds that the expert report . . . . fails to account adequately for contrary evidence, and that this methodology is not reliable or scientifically sound.").

Furthermore, Dr. Abramson was unwilling to state this opinion outside of litigation, raising concerns about whether he "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). Dr. Abramson worked for Wells Fargo Insurance Services (WFIS) from 2005 to 2012. (Dkt. No. 974-1 at 291). In his role there, Dr. Abramson provided advice about how to "[r]educe unnecessary spending on pharmaceutical products." (*Id.* at 293). In particular, he "would try to identify medicine that [he] thought . . . were either overprescribed or perhaps prescribed for purposes that were not necessary." (*Id.* at 294). However, during his entire tenure with WFIS, he never recommended that customers should not reimburse for Lipitor prescribed for primary prevention in women. (*Id.* at 295, 296).

During the time that Dr. Abramson worked for WFIS, he was testifying in litigation that Lipitor was not effective for primary prevention in women. (*Id.* at 297). However, he "never told a client that this drug doesn't work for primary prevention." (*Id.* at 298). Dr. Abramson testified that there were "boundaries" in his work with WFIS that do not exist with litigation, and

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of Lipitor to "[r]educe the risk for revascularization procedures and angina." (Dkt. No. 970-28 at 4).

that litigation is a "different forum" from his continuing medical education presentations. (*Id.* at 300). Dr. Abramson testified that he feels comfortable saying things in litigation that would not feel comfortable saying to his clients at WFIS. (*Id.*).

The Court is highly suspect of an opinion that Dr. Abramson does not feel comfortable espousing to clients outside of the courtroom. After all, *Daubert* "requires the district judge to satisfy himself that the expert is being as careful as he would be in his regular professional work outside his paid litigation consulting." *Sheehan v. Daily Racing Form, Inc.*, 104 F.3d 940, 942 (7th Cir. 1997); Fed. R. Evid. 702, advisory committee's note (2000 amendments); *see also In re Ephedra Products Liab. Litig.*, 393 F. Supp. 2d 181, 189 (S.D.N.Y. 2005) ("The analogies, inferences and extrapolations connecting the science to the witness's conclusions must be of a kind that a reasonable scientist or physician would make in a decision of importance arising in the exercise of his profession outside the context of litigation."). Therefore, for the reasons stated above, the Court finds Dr. Abramson's "no evidence" opinion inadmissible under Rule 702.

Dr. Abramson states one other opinion in deposition that the Court must address here.[21] In deposition, he testifies that "I don't think the FDA should have approved Lipitor for primary prevention in women." (Dkt. No. 970-5 at 25; *see also* id. at 20 ("I would not have Lipitor be indicated for primary prevention in women."); *id.* at 20 ("Q. ...[Y]ou think that Lipitor prescriptions for women for primary prevention should be an off-label use. Is that right? A. Yes.")). Plaintiffs, however, do not make such an argument and "do not allege that Lipitor . . . should never have been approved for use by women." (Dkt. No. 1046 at 33). This case concerns the appropriateness of Defendant's actions, not the FDA's action. Therefore, this opinion is

[21] Defendant makes a number of other arguments regarding Dr. Abramson's opinions by separate motion. (Dkt. No. 974). The Court addresses those arguments by separate order.

excluded under Fed. R. Evid. 402 and 403. The Court otherwise reserves ruling on Dr. Abramson's opinions until addressing the full motion concerning his report and opinions. (*See* Dkt. No. 974).

IV. Conclusion

For the reasons stated above, Defendant's Motion to Exclude Expert Testimony and Claims that Lipitor is Not Effective for and Should Not Be Approved for Primary Prevention in Women, (Dkt. No. 970), is **GRANTED IN PART AND DENIED IN PART**.

To the extent that Plaintiffs claim a state law duty required Defendant to include different statements on Lipitor's label regarding Lipitor's efficacy for primary prevention in women based on (1) the ASCOT data or (2) information solely related to the risk of diabetes, those claims are preempted and **DISMISSED**. Defendant's motion with regard to preemption is otherwise **DENIED**.

Defendant's motion to exclude Dr. Wells' re-analysis of the ASCOT data under Rule 702 is **DENIED**. Defendant's motion under Rule 702 to exclude Dr. Wells's, Dr. Roberts's, and Dr. Quon's, and Dr. Abramson's opinions that (1) there is no evidence that Lipitor and/or statins are effective for primary prevention in women and (2) that Lipitor and/or statins are ineffective for primary prevention in women is **GRANTED**. Dr. Fleming's opinion that "the ASCOT data did not establish efficacy of Lipitor in women for primary prevention, and the label was misleading on this point" is **EXCLUDED** under Fed. R. Evid. 402 and 403. Dr. Abramson's opinion that Lipitor should not have been approved by the FDA for primary prevention in women is **EXCLUDED** under Fed. R. Evid. 402 and 403.

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AND IT IS SO ORDERED.

Richard Mark Gergel
United States District Court Judge

May 6, 2016
Charleston, South Carolina