UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF KENTUCKY
CENTRAL DIVISION
LEXINGTON

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| IN RE: ONGLYZA (SAXAGLIPTIN) AND KOMBIGLYZE XR (SAXAGLIPTIN AND METFORMIN) PRODUCTS LIABILITY LITIGATION | Master File No. 5:18-md-2809-KKC<br>MDL No. 2809<br>ALL CASES |

**OPINION AND ORDER ON MOTIONS TO EXCLUDE EXPERTS**
**(DE 626, 630, 633, 635)**

This matter is before the Court on the parties' motions to exclude expert testimony. The plaintiffs have moved to exclude three of the defendants' experts: Drs. Suneil Koliwad (DE 630)[1], Eric Adler (DE 633), and Todd Lee (DE 635).[2] The defendants have moved to exclude one of the plaintiffs' experts: Dr. Parag Goyal (DE 626).

The parties have fully briefed the motions. This Court and the Superior Court of California, which is presiding over the coordinated proceedings in California state court, conducted joint hearings, after which the parties filed supplemental briefs. For the following reasons, the Court will grant the motion to exclude Dr. Goyal and will deny the remaining motions.

## I. Background

This action is a multidistrict litigation that involves medications that the defendants manufacture, which are aimed at treating type 2 diabetes. The medications are Onglyza

[1] All docket entry (DE) numbers refer to the docket entry numbers in the MDL Master File, 5:18-2809.
[2] Plaintiffs have also moved to exclude the testimony of defense expert Dr. Michael Fowler (DE 630). Dr. Fowler was unable to attend the hearings the week of August 9, 2021 due to a serious illness. Accordingly, the Court ruled it would conduct the hearing on the motion to exclude him at a later date. (DE 696, Order.)

and Kombiglyze, both of which contain saxagliptin as an active ingredient. Onglyza is the brand name under which saxagliptin is sold. Kombiglyze is a single pill that combines saxagliptin and metformin, another diabetes medication. (DE 635-10, Adler Report at 11.)

The plaintiffs allege that saxagliptin caused them to suffer heart failure and other conditions. The Court bifurcated discovery into two phases with the first phase addressing the general causation issue, i.e., whether saxagliptin can cause any person to develop heart failure or the other conditions alleged by the plaintiffs. (DE 179, Case Mgmt. Order.) Each of the experts targeted on these motions opines on that issue.

### A. Saxagliptin

Saxagliptin is one of several drugs in a class of medications known as dipeptidyl peptidase-4 inhibitors ("DPP-4 inhibitors"). (DE 626-27, Abraham Report at 14.) This class of drugs is generally a second-line treatment for diabetes patients. *Id*. Physicians often initially prescribe metformin to diabetic patients because of "its long history of efficacy, safety, and tolerability." *Id*. at 15. If metformin no longer sufficiently controls glucose levels, then physicians will often add a second-line medication such as a DPP-4 inhibitor. Other classes of second-line medications are thiazolidinedione (TZD), sulfonylurea (SU), and a sodium-glucose cotransporter-2 inhibitor (SGLT-2 inhibitor). *Id* at 15. Prescribing multiple drugs to diabetic patients is common because the "the disease is progressive, so that a single medication or medication combination that previously provided adequate glucose control no longer does." *Id*.

### B. Bradford Hill causation analysis

In reaching their opinions on causation, each of the experts at issue employed what is known as the "Bradford Hill" analysis to determine whether the available data indicates that exposure to saxagliptin can cause an increased risk of hospitalization for heart failure. The analysis is meant to apply when "observations reveal an association between two

variables." It addresses the aspects of that association that researchers should analyze "before deciding that the most likely interpretation of [the association] is causation." (DE 626-41, Bradford Hill article at 295.) The framework was developed by epidemiologist Sir Austin Bradford Hill, who identified nine factors that he "suggested were particularly relevant for assessing whether an observed association may be causal." (DE 635-10, Adler Report at 30.) "These nine factors are standard features generally considered relevant for determining whether an apparent association is causal." (DE 626-27, Abraham Report at 35-36.) The nine factors are:

1) **Strength of association**: this factor asks how strong the alleged association is between exposure to the drug and the outcome. (DE 626-27, Abraham Report at 36.) The strength of association is measured by relative risk. The higher the relative risk, the greater the likelihood that relationship is causal and the less the likelihood that chance, bias, or any "confounding factor" might account for the association. Federal Judicial Center, Reference Manual on Scientific Evidence (3rd Ed. 2011) 572, 602. "Confounding occurs when another causal factor (the confounder) confuses the relationship between the agent of interest and outcome of interest." *Id.* at 591. A relationship "is deemed confounded [] where there is a third factor that is related to both the exposure and the outcome that can result in it looking like there is an association when one does not exist. One classic example is the association between ice cream sales and sunburns. It is not ice cream sales that causes the sunburns." DE 631-3, Lee Report at 7.) Instead, there is a "confounder," namely sunny weather that is related to both the ice cream sales and sunburns. *Id.* at 8.

2) **Consistency of association**: this factor asks, has the observed association "been repeatedly observed by different persons, in different places, circumstances and times?" (DE 626-41, Bradford-Hill article at 296.) Researchers look at "whether the association has been found consistently across studies." (DE 626-27, Abraham Report at 38.) "Consistency is upheld when the same finding is shown in multiple studies across different populations and settings." (DE 628-3, Goyal Report at 9.) "Rarely, if ever, does a single study persuasively demonstrate a cause-effect relationship." Reference Manual on Scientific Evidence at 604. It is important that a study be replicated in different populations and by different investigators before a causal relationship is accepted by epidemiologists and other scientists. *Id.*

3) **Specificity**: "The questions asked in evaluating specificity of the association are: 1) does the event ever occur without the exposure; and 2) does the exposure ever happen without the event occurring?" (DE 631-3, Lee Report at 30-31.) "Although perfect specificity almost never exists, the degree of specificity can be informative. For instance, if the vast majority of events occur without the

exposure, and the vast majority of exposures do not result in the event, these factors weigh against causation." *Id.* at 31.

4) **Temporal relationship**: this factor asks whether the exposure occurred before the outcome. "If an exposure causes disease, the exposure must occur before the disease develops. If the exposure occurs after the disease develops, it cannot have caused the disease." Reference Manual on Scientific Evidence 601. A temporal relationship is necessary but not sufficient to find a causal relationship between exposure and outcome (DE 626-27, Abraham at 40; DE 630-3, Koliwad at 51.)

5) **Biological gradient**: this factor asks whether there is a "dose-response" relationship between exposure and outcome, namely "whether patients who take a higher dose of a medication are more likely to develop heart failure than patients who take a lower dose." (DE 630-3, Koliwad at 52.) "[I]f causation is present, higher exposure should either [] more likely lead to the outcome or lead to more severe outcome." (DE 628-3, Goyal Report at 11.)

6) **Biological plausibility**: this factor "is focused on whether or not the observed association make sense given what we know about the disease and the exposure." (DE 631-3, Lee Report at 32.) For this factor, researchers consider "existing knowledge about human biology and disease pathology to provide judgment about the plausibility that an agent causes a disease." Reference Manual on Scientific Evidence 620.

7) **Coherence**: this factor asks whether "a causal relationship between saxagliptin and new or worsened heart failure would be coherent with our current understanding of either saxagliptin's effects, or coherent with our understanding of heart failure and its mechanisms." (DE 626-27, Abraham Report at 42.) The "cause-and-effect interpretation of [] data should not seriously conflict with the generally known facts of the natural history and biology of the disease." (DE 626-41, Bradford Hill article at 298.)

8) **Experiment**: this factor asks "whether removing an exposure affects the likelihood of the outcome occurring." (DE 630-3, Koliwad at 56.) "If an agent is a cause of a disease, then one would expect that cessation of exposure to that agent ordinarily would reduce the risk of the disease." Reference Manual on Scientific Evidence at 605.

9) **Analogy**: this factor asks whether exposure to analogous medications can cause the outcome. (DE 626-27, Abraham Report at 43.) "[W]hen one medication within a class has been found to cause an adverse event, this finding may help inform causation assessments for other medications in the class. Similarly . . . the absence of analogous effects in other medications of the same class or with the same mechanism of action weighs against finding a causal relationship between the original medication and outcome." (DE 631-3, Lee Report at 33.)

### C. Available data regarding Saxagliptin and heart failure

As to the data regarding saxagliptin that was available for the experts in their Bradford Hill analyses, medications undergo various studies to evaluate whether they are associated with a risk. (DE 631-3, Lee Report at 4.) One such study is a randomized controlled trial (RCT), in which the subjects are "randomly assigned to one of two groups: one group exposed to the agent of interest and the other not exposed." Reference Manual on Scientific Evidence 555. This kind of study is considered "the gold standard for determining the relationship of an agent to a health outcome or adverse side effect." *Id*. This is because, "[r]andomization minimizes the likelihood that there are differences in relevant characteristics between those exposed to the agent and those not exposed." *Id*. An RCT is the "best way to ensure that any observed difference in outcome between the two groups is likely to be the result of exposure to the drug or medical treatment." *Id*. Some such studies are single blinded, meaning the patient does not know which treatment he or she is receiving, and some are doubled blinded, meaning that neither the researcher nor the patient know which treatment the patient is receiving. (DE 631-3, Lee Report at 6.)

A second kind of study is an observational study, in which the drug is not prescribed randomly but as part of a clinical practice. *Id*.at 4. The "investigator identifies a group of subjects who have been exposed and compares their rate of disease or death with that of an unexposed group." Reference Manual on Scientific Evidence 556. One disadvantage of this study as compared to an RCT is that an RCT can control for potential risk factors. The researcher cannot directly control for these risk factors in an observational study. The researcher can, however, address the possible role of risk factors by considering them in the design of the study and in the analysis and interpretation of the results. *Id*.

One type of observational studies is a cohort study. A "cohort" is a "designated group of persons followed or traced over a period of time to examine health or mortality

experience." Reference Manual on Scientific Evidence at 621. A cohort study follows two groups of patients – those who have taken medication and those who have not – and then measures and compares the incidence of the disease in the two groups. *Id*. at 557.

A third kind of study is a meta-analysis, which is "a systematic review" of multiple studies. (DE 631-3, Lee Report at 7.) "Meta-analysis is a method of pooling study results to arrive at a single figure to represent the totality of the studies reviewed." Reference Manual on Scientific Evidence at 607.

Finally, animal studies may be used to determine toxicity in humans. *Id*. at 563.

Each of these kinds of evidence carries different weight in a causation analysis. At the *Daubert* hearing, the experts described a "pyramid" of evidence with the bottom consisting of evidence that carries the least weight in a causational analysis and the top consisting of evidence that carries the most weight. (Pfs.' Ex. 10; DE 707, Wells Test. at 40.) At the bottom of the pyramid are animal studies. (DE 707, Well Test. at 41-42.) Above animal studies are observational studies. *Id*. at 43-44. At the top of the pyramid are RCTs, with double-blinded RCTs at the very top. *Id*.at 46.

**1) Pre-FDA approval pre-clinical animal studies and clinical trials**

Defendants assert that, prior to the FDA approval of saxagliptin, they conducted over 100 pre-clinical studies of saxagliptin involving thousands of animals and also conducted various clinical trials involving thousands of human patients. (DE 628, Mem. at 2.) None of these studies found that saxagliptin posed any cardiovascular risk or that it increased the risk of heart failure. (DE 626-4, Pollack 2017; DE 626-5, Iqbal 2014; 626-6, FDA Medical Review). Thus, the U.S. Food and Drug Administration (FDA) approved Onglyza on July 31, 2009 and Kombiglyze on November 5, 2010. (DE 363-6, 363-7, FDA Approval Letters.)

**2) SAVOR study (2013)**

In 2008, the FDA required that sponsors conduct cardiovascular outcomes trials ("CVOTs") for medications aimed at treating type 2 diabetes. (DE 630-3, Koliwad Report at 23.) The so-called SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) study of saxagliptin was a large RCT published in 2013. It involved 16,492 patients with Type 2 diabetes who were followed for a median of 2.1 years. (DE 626-27, Abraham Report at 16.) It was a double-blinded, randomized clinical trial studying saxagliptin and cardiovascular outcomes in high-risk patients. (DE 626-27, Abraham Report at 16.)

SAVOR tested for multiple endpoints. The primary endpoints included cardiovascular death, non-fatal myocardial infarction, and non-fatal ischemic stroke. There were also multiple secondary endpoints including hospitalization for heart failure. (DE 626-27, Abraham Report at 16-17; DE 646-11, Scirica 2013 at 1319.) SAVOR found no statistically significant difference between saxagliptin and placebo with regard to any endpoint except hospitalization for heart failure. (DE 626-27, Abraham Report at 17.) Of patients who received saxagliptin in the SAVOR trial, 3.5 percent were hospitalized for heart failure compared to 2.8 percent of patients who received the placebo. (DE 646-19, FDA Drug Safety Communication.) In other words, "35 out of every 1,000 patients compared to 28 out of every 1,000 patients." *Id*. The association between saxagliptin and hospitalization for heart failure appeared at the six-month treatment mark and then dissipated within 10 to 11 months of treatment. (DE 626-27, Abraham Report at 17.)

As a result of the SAVOR finding, the FDA added new warnings about the risk of hospitalization for heart failure to saxagliptin drug labels. (DE 646-19, April 5, 2016, FDA Drug Safety Communication.) The warning states, "In a cardiovascular outcomes trial enrolling participants with established [atherosclerotic cardiovascular disease (ASCVD)] or

multiple risk factors for ASCVD (SAVOR Trial), more patients randomized to ONGLYZA (289/8280, 3.5%) were hospitalized for heart failure compared to patients randomized to placebo (228/8212, 2.8%)." (Pfs.' Ex. 5, ONGLYZA prescribing information.) The warning continues, "Consider the risks and benefits of ONGLYZA prior to initiating treatment in patients at a higher risk for heart failure." *Id*.

**3) CVOTs of other DPP-4 inhibitors**

Consistent with the FDA requirement, CVOTs were also conducted on other DPP-4 inhibitors. These trials (and the DPP-4 inhibitor studied) were EXAMINE (alogliptin), TECOS (sitagliptin), CARMELINA (linagliptin), CAROLINA (linagliptin), and VIVIDD (vildagliptin). (DE 630-3, Koliwad Report at 29-30.) The outcomes of all these CVOTs, including SAVOR, "were remarkably similar" except for SAVOR's finding regarding hospitalization for heart failure. *Id*. None of these CVOTs showed that DPP-4 inhibitors posed a statistically significant risk of heart failure. (DE 710, Goyal Test. at 107.)

**4) Post-SAVOR studies**

As discussed, the SAVOR study tested for multiple endpoints. A problem with testing for multiple endpoints is that "the more statistical tests conducted, the greater likelihood of having at least one false positive where the result is statistically significant by chance." (DE 631-3, Lee Report at 13.) For example, "when you list the signs of the zodiac, if you add enough things, you can find an association between Libras and heart disease. It doesn't mean that really exists. It's just if you list enough things, you may find an association. That does not establish causation." (DE 712, Adler Test. at 29.)

Thus, the SAVOR authors explained that "the observation of a higher incidence of hospitalization for heart failure among patients treated with saxagliptin was unexpected and should be considered within the context of multiple testing that may have resulted in a false positive result." (DE 646-11, Scirica 2013 at 1324.) The authors cautioned, "[t]his

finding merits further investigation and needs to be confirmed in other ongoing studies, and a class effect should not be presumed." *Id*. In a follow-up study, the authors stated that, "[a]lthough unexpected, the incremental risk of heart failure hospitalization observed with saxagliptin is likely valid, given the large number of events and the prespecification of heart failure hospitalizations as a component of the secondary endpoint, together with central blinded adjudication." (DE 626-10, Scirica 2014 at 1585.) The authors again cautioned, however, that "the observation of an increased risk of hospitalization for heart failure with saxagliptin must be taken in the context of multiple testing and the risk of a 'false-positive' result, although there was a statistically significant difference between the 2 groups after post hoc adjustment for multiple comparisons." *Id*.

Consistent with the SAVOR authors' urging, five sets of researchers undertook observational studies of saxagliptin after SAVOR was published: 1) Fu et al., 2016; 2) Toh et al., 2016; 3) Fadini, et al., 2017; 4) Chang et al, 2016; and 5) Kim 2017. None of them found an association between saxagliptin and heart failure. (DE 635-10, Adler Report at 20; Defs.' Ex. 10; DE 710, Goyal Test. at 87-88, 91, 99.) There were also multiple observational studies that examined the risk of heart failure posed by other DPP-4 inhibitors. "Overall, the vast majority of these studies found no association between heart failure and the DPP-4 inhibitor(s) under examination." (DE 635-10, Adler Report at 29.)

In addition to the observational studies, several research groups performed meta-analyses of saxagliptin and DPP-4 inhibitor clinical trials. The meta-analyses of saxagliptin found no increased risk of heart failure when SAVOR data was excluded. (DE 630-3, Koliwad Report at 38; DE 626-27, Abraham Report at 31; Defs.' Ex. 9, Iqbal 2014, Discussion.) Other meta-analyses were conducted on class-wide DPP-4 inhibitor data. The most recent of these are Singh et al. (2019) and Sinh et al. (2019), both of which found no

increased risk of hospitalization for heart failure among DPP-4 inhibitor users. (DE 630-3, Koliwad at 38; DE 626-27, Abraham Report at 31.)

**II. Analysis**

Under Federal Rule of Evidence 702, expert testimony will be admitted where the proponent shows that it satisfies three requirements. "First, the witness must be qualified by 'knowledge, skill, experience, training, or education.'" *In re Scrap Metal Antitrust Litig.*, 527 F.3d 517, 529 (6th Cir. 2008) (quoting Fed. R. Evid. 702). "Second, the testimony must be relevant, meaning that it 'will assist the trier of fact to understand the evidence or to determine a fact in issue.'" *Id*. "Third, the testimony must be reliable." *Id*. The party proffering the expert has the burden of proving by a preponderance of the evidence that the expert satisfies Rule 702. *Sigler v. Am. Honda Motor Co.*, 532 F.3d 469, 478 (6th Cir. 2008).

As to reliability, in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), "the Court charged trial judges with the responsibility of acting as gatekeepers to exclude unreliable expert testimony." Fed. R. Evid. 702, advisory committee notes to 2000 amendment. Rule 702 provides "general standards to assess reliability: whether the testimony is based upon 'sufficient facts or data,' whether the testimony is the 'product of reliable principles and methods,' and whether the expert 'has applied the principles and methods reliably to the facts of the case.'" *In re Scrap Metal Antitrust Litig.*, 527 F.3d at 529 (quoting Fed. R. Evid. 702).

A court's inquiry must focus "solely on principles and methodology, not on the conclusions they generate." *Daubert*, 509 U.S. at 595. "The task for the district court in deciding whether an expert's opinion is reliable is not to determine whether it is correct, but rather to determine whether it rests upon a reliable foundation, as opposed to, say, unsupported speculation." *In re Scrap Metal Antitrust Litig.*, 527 F.3d at 529-30. Courts should confirm that "the factual underpinnings of the expert's opinion [are] sound,"

*Greenwell v. Boatwright*, 184 F.3d 492, 498 (6th Cir. 1999), but generally "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." *Daubert*, 509 U.S. at 596. "Rule 702 should be broadly interpreted on the basis of whether the use of expert testimony will assist the trier of fact." *Morales v. Am. Honda Motor Co.*, 151 F.3d 500, 516 (6th Cir. 1998) (citation omitted). "Mere weaknesses in the factual basis of an expert witness's opinion . . . bear on the weight of the evidence rather than on its admissibility." *McLean v. 988011 Ontario, Ltd.*, 224 F.3d 797, 801 (6th Cir. 2000) (quotations and citation omitted); *United States v. Davis,* 103 F.3d 660, 674 (8th Cir. 1996) (noting defendant was "free to challenge the expert's conclusions and point out the weaknesses of the [expert's] analysis to the jury during cross-examination" but "[w]eight and credibility are the province of the jury.")

### A. Plaintiffs' motion to exclude the testimony of Dr. Suneil Koliwad (DE 630)

Defense expert Suneil Koliwad is a medical doctor with a Ph.D. in molecular physiology. He is a board-certified endocrinologist and a clinical researcher and associate professor at the University of California at San Francisco (UCSF) School of Medicine's Diabetes Center, where he is also the Chief of the Division of Endocrinology. (DE 630-4, Koliwad CV; DE 630-3, Koliwad Report at 1-2.) Dr. Koliwad opines that "the evidence does not support the presence of a causal relationship between saxagliptin use and heart failure." (DE 630-3, Koliwad Report at 1, 45.)

In his report, Dr. Koliwad explains that, in assessing whether there is a causal relationship between saxagliptin and heart failure, he employed the same methodology that he uses when making causal assessments in his regular clinical practice and scientific research. *Id.* at 45. As discussed, like all the experts at issue on these motions, Dr. Koliwad

employed the Bradford Hill criteria to assesses the causal link. In assessing the Bradford Hill factors, Dr. Koliwad considered SAVOR, the CVOTs of other DPP-4 inhibitors, the post-SAVOR observational studies of saxagliptin and other DPP-4 inhibitors, and the meta-analyses of saxagliptin and other DPP-4 inhibitors. *Id*. at 23-29.

In their motion to exclude Dr. Koliwad's testimony, the plaintiffs do not question his methodology. Instead, they argue that he is not qualified to opine on whether saxagliptin can cause heart failure because he is an endocrinologist who has no expertise in cardiology. (DE 630-1, Mem. at 1.) Plaintiffs argue that, as an endocrinologist, Dr. Koliwad does not treat heart failure. Instead, he refers his patients with heart failure to a cardiologist for treatment.

Dr. Koliwad testified that endocrinology is "the study of diseases related to dysfunctions and/or imbalances in hormones and the impact that those dysfunctions or imbalances have on tissues throughout our body, including the cardiovascular system" and the heart. (DE 712, Koliwad Test. at 191.) Dr. Koliwad testified that he regularly treats people with diabetes as part of his clinical practice. *Id*. at 191-92. He testified that over 80 percent of his patients have diabetes, and that diabetes treatment and management is the core of his clinical practice. *Id*. He further testified that about 50 percent of his diabetes patients have cardiovascular disease and that about 20 to 25 percent of those patients have heart failure. *Id*. at 200.

As part of his treatment of diabetes patients, Dr. Koliwad must prescribe medicines to them. *Id*. at 201. In making prescribing decisions, Dr. Koliwad must understand and consider the risks and benefits of the medications. *Id*. at 201-02. Among the medications that Dr. Koliwad prescribes are DPP-4 inhibitors including saxagliptin. *Id*. at 202. He testified that prescribing this class of medications is "central" to his practice. *Id*. at 207.

Plaintiffs argue that Dr. Koliwad testified that he prescribes saxagliptin for only two to three patients each year and, therefore, is not qualified to assess whether the scientific literature indicates that it can cause heart failure. *Id*. at 229. Regardless of the number of times that Dr. Koliwad prescribes saxagliptin, he testified that he was very familiar with the risks and benefits of DPP-4 inhibitors, including saxagliptin, before becoming involved in this litigation. *Id*. at 202. As part of his practice, he was familiar with the SAVOR study and the issue of whether saxagliptin contributes to heart failure. *Id*. at 208. Dr. Koliwad testified that assessing the scientific literature to determine whether it shows that saxagliptin can cause heart failure, as he did in this case, is "emblematic" of the kinds of questions he addresses in his regular clinical practice as an endocrinologist and diabetes specialist. *Id*. at 233. Thus, Dr. Koliwad's testimony in this case is about a matter "growing naturally and directly out of research [he has] conducted independent of the litigation." *In re Meridia Prod. Liab. Litig.*, 328 F. Supp. 2d 791, 804 (N.D. Ohio 2004) (quoting advisory committee notes to Fed. R. Evid. 702.)

Moreover, Dr. Koliwad has extensive experience in clinical research and, thus, is qualified to assess current research related to whether saxagliptin can cause heart failure. Dr. Koliwad conducts diabetes research at UCSF's School of Medicine's Diabetes Center. (DE 630-3, Report at 1.) He conducted advanced research on cardiovascular disease for seven years (2004-11). *Id*. at 2. He has been the director of the Koliwad Laboratory in the UCSF Diabetes Center since 2011. *Id*. at 3. He is a member of the American Society of Clinical Investigators, (DE 712, Koliwad Test. at 196), and is a peer reviewer for numerous journals, meaning he critiques medical and scientific studies. (DE 630-3, Report at 4.)

Plaintiffs argue that Dr. Koliwad's research and laboratory work have not focused on heart failure or its causes. He testified, however, that as part of his work as a researcher,

he regularly reviews clinical research and scientific literature focusing on diabetes medications and their impact on the vascular system and heart. (DE 712, Tr. at 196.) Accordingly, Dr. Koliwad is qualified to assess current scientific evidence and render an opinion on whether it supports "the presence of a causal relationship between saxagliptin and heart failure." (DE 630-3, Report at 1.) Plaintiffs may attack Dr. Koliwad's opinion by pointing out on cross examination that he is not a cardiologist, but the Court cannot find that only a cardiologist can analyze studies related to saxagliptin and heart failure to determine whether they indicate a causal association pursuant to the Bradford Hill criteria.

The motion to exclude Dr. Koliwad's testimony will be denied.

**B. Plaintiffs' motion to exclude Dr. Eric Adler's testimony (DE 633)**

Plaintiffs move to exclude the expert testimony of Dr. Eric Adler, a board-certified cardiologist who practices at University of California San Diego (UCSD) Hospital and is a medical professor at UCSD. In his cardiology practice, Dr. Adler cares for patients experiencing heart failure, 30 percent of whom have diabetes. (DE 635-10, Adler Report at 1-3.) Like Dr. Koliwad, Dr. Adler employed the Bradford Hill criteria to analyze the relevant scientific studies and literature and concluded that "there is insufficient evidence to demonstrate a causal relationship between saxagliptin use and either new heart failure or worsened heart failure." *Id*. at 1.

Plaintiffs argue that it is unlikely that Dr. Adler wrote his report. They argue that Dr. Adler's opinion is a "near replica" of the report of Dr. William T. Abraham, who is another defense expert. (DE 634-1, Mem. at 2.) Plaintiffs argue that the reports of Drs. Adler and Abraham cite many of the same sources, cover many of the same topics, and that the "syntax, sentence structure, and organization" of the reports are "virtually identical." (DE 668, Reply at 21.)

In his deposition and at the hearing, Dr. Adler testified that he had not even read Dr. Abraham's report or the report of any other defense expert. (DE 644-1, Adler Dep. at 21; DE 712, Hr'g Tr. at 46.) Likewise, Dr. Abraham testified in his deposition that he had never spoken with Dr. Adler about this matter and had not reviewed Dr. Adler's expert report. (DE 642-14, Abraham Dep. at 56-57.) Dr. Adler testified at his deposition and at the hearing that he wrote his report and that he did not use a ghost writer although defense counsel did edit sentence structure and formatting. (DE 644-1, Adler Dep. at 51-52; DE 712 at 45.) Plaintiffs give the Court no reason to question that testimony.

Drs. Adler and Abraham are both cardiologists and both have been asked to proffer an opinion on the same issue: whether saxagliptin can cause heart failure. As would be expected, both consulted the finite body of literature relevant to that question. It is not surprising that they cite many of the same sources. As to plaintiffs' argument that the reports of the two doctors contain the same phrases, most of the phrases plaintiffs cite in support of this argument are exact quotes from the relevant literature as indicated by the internal quotations and citations in the sample quotes from the doctors' reports cited by the plaintiffs. (DE 634-1, Mem. at 10.) Dr. Adler did not copy Dr. Abraham's sentences in these instances as plaintiffs argue. Instead, both doctors quoted the relevant literature.

Plaintiffs also argue that Dr. Adler incorrectly relied on the MEASURE-HF study, which they argue is "scientifically inferior data" when compared to the SAVOR study. The Court ruled at the *Daubert* hearings that neither party may use the MEASURE-HF study either to support its own case or to attack the opposing party's case. This is because the study has still not been published and it would be confusing to ask jurors to consider an incomplete study that is not yet published in reliable medical journals. (DE 710, Tr. at 186-87.) Accordingly, at trial, Dr. Adler will not be permitted to rely on the MEASURE-HF study.

The Court's ruling that no party may rely on MEASURE-HF does not require that Dr. Adler's opinion be excluded because he did not rely solely on the MEASURE-HF study in formulating his opinions. Dr. Adler considered the scientific data discussed above consisting of the SAVOR trial, the observational studies that used "real-world data" to examine saxagliptin and heart failure after the SAVOR study, and the meta-analyses of clinical trials examining saxagliptin and heart failure, and the CVOTs and meta-analyses of other DPP-4 inhibitors. (DE 635-10, Report at 13-29),

Plaintiffs also argue that Dr. Adler is not qualified to opine that the authors of the SAVOR study should have applied the so-called "Bonferroni correction" differently. (DE 634-1, Mem. at 12-13.) The Bonferroni correction is a statistical adjustment used to correct for the risk described above of a false positive when a clinical trial tests for multiple endpoints. (DE 712, Adler Test. at 29-31.) Dr. Adler explained that he teaches medical students how to adjust for multiple endpoints, or multiplicity, and that it is a "central question" he addresses when designing trials. (DE 712, Adler Test. at 29.)

As discussed, the SAVOR authors identified three primary endpoints and three secondary endpoints of the study. (DE 646-11, SAVOR 2013 at CM-ECF p. 4.) Thus, they published a follow-up study that applied a post-hoc adjustment for six endpoints. (DE 626-10, SAVOR 2014 at 1580.) Dr. Adler opines that the SAVOR authors should have adjusted for 11 endpoints. (DE 635-10, Adler Report at 17.) He testified at the hearing that there were actually 11 tests performed and that, when the test results are adjusted for 11 endpoints, SAVOR shows no association between saxagliptin use and hospitalization for heart failure. (DE 712, Adler Test. at 33; DE 635-10, Adler Report at 18.) Dr. Adler testified that he was familiar with at least three other papers by scientists who had similarly criticized the Bonferroni correction applied by the SAVOR authors. (DE 712, Adler Test. at

34-35; Defs.' Ex. 34.) His report discusses Pocock 2016, Centrian-Cuenca 2016, and Scheen 2018. (DE 635-10, Adler Report at 18.)

Plaintiffs argue that Dr. Adler is not qualified to opine on how the Bonferroni correction should be applied because he does not have experience in applying it. Defendants point out that Dr. Adler has extensive research experience, including 20 years of experience in conducting clinical trials. (DE 712, Adler Test. at 7.) Dr. Adler testified that he has been involved in designing clinical trials and generating hypotheses; monitoring clinical trials while they are proceeding to make sure that they are being performed adequately and accurately; and assisting with the interpretation and presentation of trial results when they are concluded. *Id*.

He leads the Adler Lab at UCSD, which is a research lab devoted to studying how genetic mutations cause cardiomyopathy. Further, he has participated in the design and evaluation of preclinical primate studies and has been the principal investigator in numerous clinical trials studying all stages of heart failure. In addition, he participates in the peer-review process for numerous medical journals. (DE 635-10, Report at 2.)

At the hearing, Dr. Adler testified that he had experience dealing with adjustments for multiplicity in clinical trials. (DE 712, Adler Tr. at 30.) He did testify in his deposition that he relies on a biostatistician to apply a Bonferroni correction in his own research and that he was unsure if he had ever applied the correction himself. (DE 634-2, Adler Dep. at 116.) When asked further questions about applying the Bonferroni correction, he conceded it was not his "complete area of expertise." (DE 634-2, Adler Dep. at 122.)

Nevertheless, at the hearing, Dr. Adler gave step-by-step instructions regarding how the correction is applied. (DE 712, Adler Test. at 32.) Further, applying the correction is relatively straightforward. As Dr. Adler explained, it consists of dividing the false-positive rate by the number of endpoints. In other words, applying the correction involves "dividing

one number by another." (DE 712, Adler Tr. at 33.) Dr. Adler's opinion that an 11-point adjustment should be applied is supported by other scientists. Accordingly, the Court will permit Dr. Adler to opine that he believes an 11-point Bonferroni correction should be applied to the SAVOR study. Plaintiffs may of course point out on cross examination any deficiencies in Dr. Adler's experience or qualifications on this issue.

The Court further notes, however, that Dr. Adler's causation opinion does not depend on his application of the 11-point Bonferroni correction as plaintiffs argue. (DE 718, Post-Hr'g Br. at 6.) As Dr. Adler explained, the Bonferroni correction for 11 endpoints only affects whether the SAVOR study should be construed to find any association between saxagliptin and hospitalization for heart failure at all. (DE 712, Adler Test. at 35-36.) According to Dr. Adler, if the SAVOR study is construed to find no such association, then there is no need to undertake the Bradford Hill causation analysis because the analysis is only undertaken if there is a "clear-cut association" between an exposure and outcome. (DE 635-10, Adler Report at 30.)

Nevertheless, in his report, Dr. Adler goes on to undertake the Bradford Hill analysis, and he found no causation relationship. Thus, he testified, that "[e]ven if this association [between saxagliptin and hospitalization for heart failure from SAVOR data] was valid, it doesn't change the fact that there there's no establishment of causation." (DE 712, Adler Test. at 35-36.) Dr. Adler's Bradford Hill analysis is not affected by the Bonferroni correction, whether it is a 6- or 11-point correction.

Likewise, Dr. Adler's opinion that the SAVOR study should not be interpreted to establish causation on its own applies regardless of what Bonferroni correction is applied. Even after applying the six-point multiplicity adjustment, the SAVOR authors cautioned that the risk of a false positive remained and, thus, further testing was necessary. (DE 626-10, Scirica 2014 at 1585.) Further, Dr. Adler points out that hospitalization for heart failure

was not a primary endpoint of the study. Instead, it was a secondary endpoint and thus, not the "main focus of the trial." (DE 635-10, Adler Report at 15-16.). Dr. Adler opines that, "a statistically significant finding in a component of a secondary endpoint is considered hypothesis generating and worthy of further investigation, but is cannot be considered proof of a 'causal' relationship between use of the medication and outcome." (DE 635-10, Adler Report at 16.)

Further, Dr. Adler noted that other SAVOR findings were "inconsistent with the presence of a causal relationship between saxagliptin and heart failure." (DE 635-10, Adler Report at 18.) Dr. Adler found that "the absence of any other elevated cardiovascular risk factor," the absence of any increased risk of edema (a condition associated with heart failure), and the absence of elevated levels of NT-proBNP (a substance that is elevated in patients with heart failure) among saxagliptin patients in the study were all inconsistent with causation. (DE 635-10, Adler Report at 18-19.) Further, Dr. Adler noted that the CVOTs for other DPP-4 inhibitors did not find an elevated risk of heart failure after drug exposure and that the SAVOR authors found no clear biological mechanism by which saxagliptin could cause heart failure.

Thus, Dr. Adler opined that SAVOR should be interpreted to generate a hypothesis that "saxagliptin and heart failure may be associated in some way," but that it should not be interpreted to demonstrate a causal relationship. (DE 635-10, Adler Report at 19.) These critiques of the SAVOR study apply whether a six-point multiplicity adjustment is applied to the hospitalization finding or an 11-point adjustment. In fact, the SAVOR authors themselves offered a similar critique. As discussed, they cautioned that hospitalization-for-heart failure finding was "unexpected and should be considered within the context of multiple testing that may have resulted in a false positive result." (DE 646-11, Scirica 2013 at 1324.) The authors advised, "This finding merits further investigation and needs to be

confirmed in other ongoing studies, and a class effect should not be presumed." (DE 646-11, Scirica 2013 at 1324; DE 626-10, Scirica 2014 at 1585.)

In their post-hearing briefing, plaintiffs argue that Dr. Adler's opinion should be excluded because it "lacks reliability." (DE 718, Post-Hr'g Bf. at 5.) Plaintiffs argue that Dr. Adler's opinion largely hinges on studies that were funded by the defendants. Again, Dr. Adler's opinion relies on multiple studies. Based on the record, it appears that he considered all the studies related to saxagliptin and heart failure. Plaintiffs do not point to any studies that Dr. Adler should have considered that he did not. Nor do they point to any evidence that would allow the Court to conclude that any of the studies considered by Dr. Adler are unreliable.

Plaintiffs argue that Dr. Adler did not consider the statement of Dr. John Monyak, a biostatistician employed by the defendants, who seems to discount the need to adjust for multiplicity, stating in an e-mail, "Safety analyses usually downplay the role of multiplicity or don't consider it rigorously . . . . If you adjusted everything for multiplicity, you'd never find anything." (DE 718-5, e-mail.) Plaintiffs also argue that Dr. Adler did not consider statements at a meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committeee (EMDAC). At that meeting, an FDA pharmacist stated that, although the SAVOR study published in 2013 did not contain a multiplicity adjustment for the hospitalization-for-heart-failure endpoint, "the validity of this finding is supported by the large number of hospitalizations for heart failure events used for the estimation of risk, the fact that hospitalization for heart failure was a prespecified endpoint using a standardized definition and events were prospectively collected at end of trial and adjudicated by an independent, blinded adjudication committee." (DE 718-6, EMDAC minutes at 127.)

For his report, Dr. Adler applied the Bradford Hill analysis and considered the relevant scientific studies and literature. Plaintiffs cite to no authority indicating that

reliable scientific methodology requires him to also consider particular e-mails or statements at a meeting. Further, as to the statement at EMDAC meeting regarding the validity of the hospitalization-for-heart failure finding in SAVOR, Dr. Adler agreed with the statement, testifying that no one disputes SAVOR's finding that the patients went to the hospital with heart failure. (DE 712, Adler Test. at 27-28.) The issue remains as to whether saxagliptin can cause heart failure. The motion to exclude Dr. Adler's testimony on that issue will be denied.

**C. Plaintiffs' motion to exclude Dr. Todd Lee's testimony (DE 635)**

Plaintiffs move to exclude the testimony of Todd Lee, PhD, who is a pharmacoepidemiologist and professor at the University of Illinois Chicago with experience in researching the safety of medications, including significant work regarding diabetes-related medications. (DE 631-3, Lee Report at 1-2.) Dr. Lee has been involved in research examining the safety of medications including observational studies, clinical trial analyses, and meta-analyses. *Id*.at 1.

In his report, Dr. Lee explains that clinical pharmacoepidemiology applies "epidemiological methods to study the effects of medication in patient populations" to "predict the effects of administering a medication to a patient." (DE 631-3, Lee Report at 3.) He testified that pharmacoepidemiology is a subdiscipline, or specialty, of epidemiology. (DE 712, Lee Test. at 91.) Dr. Lee opines that "the evidence does not support a clear-cut association between saxagliptin and an increased risk for hospitalizations for heart failure, let alone meet the much higher burden for establishing a causal association." (DE 109-3, Lee Report at 1.)

Plaintiffs argue that Dr. Lee's testimony should be excluded because he does not have a degree in pharmacoepidemiology. He has a Pharm D pharmacy degree and a Ph.D. in pharmaceutical outcomes research and pharmacoeconomics. (DE 631-4, Lee CV at CM-

ECF p. 2.) Regardless, Dr. Lee has extensive experience in pharmacoepidemiology. He teaches both undergraduate and graduate courses in the field and has published articles and given presentations on the topic. (DE 631-4, Lee CV; DE 712, Lee Test. at 94.) He testified that he has worked in the field for more than 20 years. (DE 712, Lee Test. at 91-92.) As part of that work, he has published observational studies and meta-analyses and interpreted clinical trial. (DE 712, Lee Test. at 93.) In addition, he has been recognized as a "best reviewer" by the Journal of Pharmacoepidemiology and Drug Safety, which Dr. Lee testified is the premier journal of the International Society for Pharmacoepidemiologists. (DE 712, Lee Test. at 95.)

In reaching his opinion as to whether the evidence supports an association or causation relationship between saxagliptin and heart failure, Dr. Lee employed the Bradford Hill framework and considered the SAVOR study, the CVOTs for other DPP-4 inhibitors, meta-analyses of saxagliptin and of other DPP-4 inhibitors, and observational studies. (DE 631-3, Lee Report at 11-26.) This is precisely the kind of analysis Dr. Lee performs as part of his regular work. In his report, Dr. Lee asserts that "[p]harmacoepidemiologists scrutinize all phases of clinical trials . . . , observational studies, and other evidence in evaluating the effects of medications." (DE 631-3, Report at 3.) Dr. Lee testified that the "primary focus" of pharmacoepidemiology is determining whether drugs are associated with adverse effects on the human body. (DE 712, Lee Test. at 91.) He testified that causation analysis is part of his day-to-day work. *Id*. at 89. Further, Dr. Lee's graduate and undergraduate pharmacoepidemiology courses include instruction in the Bradford Hill analysis. (DE 712, Lee Test. at 94, 130.)

Dr. Lee is qualified to review the published literature to determine whether it supports a causal connection between saxagliptin and heart failure. The plaintiffs also argue that Dr. Lee is not qualified to render this opinion because he is not a cardiologist.

For his analysis, however, Dr. Lee was not required to diagnose heart failure. Instead, as Dr. Lee explained at the hearing, he reviewed the literature that studied the relationship between 1) saxagliptin and other DPP-4 inhibitors and 2) events that the studies' authors had identified as heart-failure events. (DE 712, Lee Test. at 170.) Dr. Lee did not himself determine if the patients involved in the study experienced heart failure.

Plaintiffs argue that Dr. Lee's testimony should be excluded because he did not employ a reliable methodology. Plaintiffs argue that Dr. Lee did not "undertake any of his own analysis" of the raw data underlying the studies included in his analysis and, instead, conducted a "literature review" of studies selected by defense counsel. (DE 635-1, Mem. at 8-9, 17.) Plaintiffs argue that Dr. Lee was required to perform his own "statistical analysis" to validate the statistical findings of the SAVOR trial, the observational studies, and the meta-analyses. (DE 729, Post-Hr'g Reply Br. at 3.) Plaintiffs cite no authority for the argument that a reliable Bradford Hill analysis requires that the expert analyze the raw data underlying the relevant studies. None of the experts in this case did so, including the plaintiffs' expert Dr. Goyal. As to whether Dr. Lee chose the studies to include in his analysis or defense counsel did, Dr. Lee testified that, while he primarily relied on the literature provided by defense counsel, he also conducted his own searches on PubMed to ensure that he had all the relevant literature. (DE 642-5, Lee Dep. at 29-30, 54-57; DE 712, Lee Test. at 167.)

In their post-hearing brief, plaintiffs argue that Dr. Lee is not "qualified to opine regarding a biologically plausible mechanism." (DE 719, Post-Hr'g Br. at 2.) As part of his Bradford Hill analysis, Dr. Lee appropriately considered whether evidence existed of some biological mechanism by which it would "make[] sense" that saxagliptin could cause heart failure. (DE 631-1, Lee Report at 32.) In assessing biologic plausibility, Dr. Lee focused on clinical trial and epidemiological evidence. (DE 631-3, Lee Report at 32.) He noted that the

SAVOR authors reported that there were "no known mechanisms by which DPPP-4 inhibition could precipitate heart failure." (DE 631-3, Lee Report at 32; DE 626-10, Scirica 2014 at 1585.) Dr. Lee made clear at the hearing that he is not opining himself on whether there is a biological reason that saxagliptin could cause heart failure, he is simply opining that the studies involving human data have not found one. (DE 712, Lee Test. at 148.) Even though Dr. Lee is not a cardiologist, he is qualified to review the relevant scientific literature and determine whether any has theorized a biologically plausible mechanism by which saxagliptin could cause heart failure.

Plaintiffs argue that Dr. Lee did not consider evidence that did not support the defendants' position. (DE 719, Post-Hr'g Br. at 5.) But Dr. Lee testified that he reviewed the reports of the plaintiffs' experts, and that they did not identify any materials that he had not reviewed. (DE 712, Hr'g Tr. at 101-02.) In his report, Dr. Lee explains the kinds of studies that he considered for his report. He considered the relevant CVOTs, observational studies (including those involving saxagliptin users and those involving users of other DPP-4 inhibitors), and meta-analysis (including saxagliptin-specific meta-analyses and meta-analysis of the DPP-4 inhibitor class.) Plaintiffs argue that Dr. Lee's reliance on pool analyses and observational studies was improper, but they cite no authority for that argument. (DE 719, Post-Hr'g Br. at 5.)

Plaintiffs argue that Dr. Lee failed to account for the limitations of observational studies. But Dr. Lee recognizes in his report that observational studies present issues with "bias and confounding . . . because the treatment is not randomly assigned, and neither the patients nor the researchers are blinded to treatment." (DE 631-3, Lee Report at 4.) Dr. Lee noted, however, that "researchers can take steps to minimize bias and confounding both during the design of the study and during the analysis of the study data." (DE 631-3, Lee Report at 4.) He further explains that the observational studies he considered follow a

"cohort study design," which is "conceptually similar to a randomized controlled trial . . . ." (DE 631-3, Lee Report at 4.) Plaintiffs do not argue that any of the observational studies Dr. Lee relied upon were flawed in some way. His consideration of them in his Bradford Hill analysis was not improper.

Plaintiffs argue that Dr. Lee relied only on class-wide observational studies for DPP-4 inhibitors that support his opinion. (DE 719, Post-Hr'g Br. at 5.) However, Dr. Lee testified that he considered all such studies but did not focus on them, choosing to focus instead on the observational studies pertaining specifically to saxagliptin. (DE 712, Lee Test. at 123.) Plaintiffs may cross examine Dr. Lee on that choice, but it is not a reason to exclude his opinion.

Plaintiffs also argue that Dr. Lee ignored the "Wu article," which is a 2014 meta-analysis by Wu et al. (DE 719, Post-Hr'g Br. at 5.) But Dr. Lee testified that he did review the Wu article. (DE 712, Lee Test. at 142.) The article is listed in Dr. Lee's report among the literature he considered. (DE 631-3, Materials Considered at CM-ECF p. 53.) Dr. Lee testified that his report did not focus on the 2014 Wu article because it does not consider any saxagliptin-specific studies and because he focused on more recent meta-analyses, which "would have been the most comprehensive collection of data." (DE 712, Lee Test. at 186-87.)

Dr. Lee explained that the early meta-analyses, like the Wu article, that found a weak association between increased risk of heart failure and the DPP-4 inhibitor class were dominated by SAVOR data. (DE 631-3, Report at 19-20.) He explains that this association disappeared in later studies that included CVOTs other than SAVOR. (DE 631-3, Report at 20.) The Wu article itself explains that its result was "dominated" by the SAVOR trial. (Pfs.' Ex. 21, Wu 2014 at 152.) Dr. Lee explained that SAVOR contributed about two-thirds of the data for the Wu study, meaning "most of the effect estimate that is measured in the

summary is due to SAVOR." (DE 712, Lee Test. at 187-88.) Plaintiffs may cross examine Dr. Lee about his discounting of the 2014 Wu article, but he gives a sound rationale for doing so. His treatment of the article does not render his opinion unreliable.

Plaintiffs argue that Dr. Lee's methodology is unreliable because he did not consider a 2018 article by Dr. Milton Packer that identified a biologically plausible mechanism by which saxagliptin and DPP-4 inhibitors could cause heart failure. (DE 710, Post Hr'g Br. at 6.) In his report, Dr. Lee concludes, "Clinal trial evidence does not support any biologically plausible relationship between saxagliptin and heart failure." (DE 631-3, Lee Report at 32.) Dr. Lee notes that, in analyzing plausibility, plaintiffs' expert Dr. Goyal relies on Packer's article. Dr. Lee discounts Packer's article because it "suggests theoretical mechanisms, but it does not provide original experimental findings." (DE 631-3, Lee Report at 32.) Further, Dr. Lee discounts Dr. Packer's proposed mechanism because it is not specific to saxagliptin. Instead, the proposed mechanism would purport to explain how the entire class of DPP-4 inhibitors pose a risk of heart failure. Dr. Lee noted that the most updated studies, however, have not even shown an association between DPP-4 inhibitors as a class and heart failure. (DE 631-3, Lee Report at 32-33; DE 712, Lee Test. at 188-89.) Dr. Lee gives sound reasons for discounting the Packer article. His treatment of the article may be a subject for cross examination, but it is not a reason to exclude his opinion.

Plaintiffs argue that Dr. Lee's methodology is unreliable because his analysis of the "biological gradient" factor of the Bradford Hill criteria is unreliable. (DE 719, Past-Hr'g Br. at 6.) Dr. Lee explains in his report that this factor looks at whether a "dose response" exists. "If the exposure is truly causing the event, it is anticipated that bigger doses of the exposure would lead to higher event rates. If this is demonstrated, then there is a 'dose-response' between the exposure and the event." (DE 631-3, Lee Report at 31-32.) Dr. Lee states, "In none of the available trials or observational studies is there clear evidence of a

dose response relationship where heart failure risk increased, or increased more, in patients using larger doses as compared to smaller doses." *Id.*at 32. Thus, in forming his opinion regarding the biological gradient factor, Dr. Lee considered available scientific evidence. This is a reliable methodology. His opinion on this issue is consistent with plaintiffs' expert Dr. Goyal, who also testified that, based on all the data, he could not find that this factor is met. (DE 710, Goyal Test. at 6, 125, 143.)

Plaintiffs argue that Dr. Lee's methodology is unsound because, in opining on the Bonferroni correction, he did not undertake his own statistical analysis of the data underlying the SAVOR study. (DE 635-1, Mem. at 10) As Dr. Lee explained, SAVOR tested for multiple endpoints and found that "hospitalization for heart failure was the only event associated with a nominally statistically significant increase." (DE 631-3, Lee Report at 12.) As has been discussed, Dr. Lee, like the other experts, testified that one problem with testing for multiple endpoints is that "the more statistical tests conducted, the greater likelihood of having at least one false positive where the result is statistically significant by chance." (DE 631-3, Lee Report at 13.)

Again, the SAVOR authors applied a six-point Bonferroni adjustment and still found a statistically significant association between saxagliptin use and hospitalization for heart failure even though the risk of a false positive remained. Like Dr. Adler, Dr. Lee opines that SAVOR pre-specified 11 endpoints. (DE 631-3, Lee Report at 13.) Dr. Lee opines that, if an 11-point adjustment is applied, the difference in heart failure for hospitalization among SAVOR's saxagliptin and placebo groups would not be statistically significant. *Id.* Thus, like Dr. Adler, Dr. Lee opines that there is no "clear cut" association between saxagliptin and an increased risk of hospitalization for heart failure. *Id.* at 27.

Plaintiffs have not demonstrated that it is necessary to review the raw data underlying a study to determine the appropriate Bonferroni correction to apply. According

to the testimony of Dr. Lee and Dr. Adler, the appropriate correction depends upon the number of endpoints that were the object of the study. In his report, Dr. Lee identifies 11 endpoints. *Id*. at 13. There is no need to review the underlying data to determine the number of endpoints. Dr. Lee states that several researchers have agreed with the 11-point correction since SAVOR's publication. He cites Pocock 2015 and Cebrian-Cuenca 2016. *Id*. Plaintiffs may present evidence that disputes the appropriateness of the 11-point correction, but they have not shown that a reliable opinion on this issue requires an analysis of the raw data underlying the study.

The Court notes, however, that, as was the case with Dr. Adler, Dr. Lee's Bradford Hill analysis is not affected by which Bonferroni correction is applied. Again, the application of the 11-point adjustment affects only whether the Bradford Hill analysis should be undertaken at all. Dr. Lee and Dr. Adler agreed that, with the 11-point correction, there is not even a statistically significant association between saxagliptin and hospitalization for heart-failure, making a causation analysis unnecessary. Like Dr. Adler, however, Dr. Lee did undertake a Bradford Hill causation analysis, which is a totally separate analysis than the Bonferroni correction. (DE 712, Lee Test. at 100.)

Finally, Plaintiffs argue that Dr. Lee "inappropriately devalues the SAVOR causation findings." (DE 729, Post-Hr'g Reply Br. at 5). The SAVOR study, however, did not make *causation findings*. As noted multiple times in this opinion, the SAVOR authors cautioned that the higher rate of hospitalization for heart failure "should be considered within the context of multiple testing that may have resulted in a false positive result." (DE 646-11, Scirica 2013 at 1324.) The authors cautioned that the "finding merits further investigation and needs to be confirmed in other ongoing studies." (DE 646-11, Scirica 1324.) Plaintiffs have not shown that Dr. Lee's conclusion that the SAVOR study presents a

risk of a false positive is contrary to reliable scientific methodology or even to the findings of the SAVOR authors themselves.

The motion to exclude Dr. Lee's testimony will be denied.

**D. Defendants' motion to exclude Dr. Parag Goyal's Testimony (DE 626)**

Defendants move to exclude the testimony of the plaintiffs' expert, Dr. Parag Goyal, who is a board-certified cardiologist and assistant professor at Weill Cornell Medicine. He is a member of both the heart-failure faculty and of the core-research faculty. Dr. Goyal's clinical interests and expertise are focused on heart failure and his research interest and expertise are focused on "the safety of medication prescribing patterns in heart failure." (DE 628-3, Goyal Report at 1.)

He opines that "it is more likely than not that saxagliptin is capable of causing heart failure." (DE 628-3, Goyal Report at 14.) Neither Dr. Goyal nor the plaintiffs have been able to identify any other expert who has reached this opinion. (DE 710, Goyal Test. at 68.) Like the defense experts, Dr. Goyal arrives at his opinion after applying the Bradford Hill criteria. "When a scientist claims to rely on a method practiced by most scientists, yet presents conclusions that are shared by no other scientist, the district court should be wary that the method has not been faithfully applied." *Lust By & Through Lust v. Merrell Dow Pharms., Inc.*, 89 F.3d 594, 598 (9th Cir. 1996). "It is the proponent of the expert who has the burden of proving admissibility. To enforce this burden, the district court can exclude the opinion if the expert fails to identify and defend the reasons that his conclusions are anomalous." *Id.*

Dr. Goyal has never published an article applying the Bradford Hill criteria. (DE 710, Goyal Test. at 124.) Nor has he ever written any paper applying the criteria except for his report in this case. (DE 710, Goyal Test. at 124.) He agreed that no published paper had

applied the Bradford Hill criteria and found that saxagliptin caused an increased risk of hospitalization for heart failure. *Id*. at 124-25.

The defendants argue that Dr. Goyal's methodology is unreliable because his Bradford Hill analysis considers only the SAVOR study and certain animal studies and disregards all the other human data, which consists of the CVOTs, observational studies and meta-analyses discussed above. Defendants further argue that Dr. Goyal is not qualified to interpret the data from animal studies.

As to Dr. Goyal's reliance on the SAVOR study to the exclusion of all other studies involving human data, Dr. Goyal testified that he was not aware of any clinical study other than SAVOR that showed an increased risk of heart failure with saxagliptin. (DE 710, Goyal Test. at 87.) In his report, he recognizes that no CVOT or randomized control trial of DPP-4 inhibitors other than SAVOR found a statistically significant association between exposure to the drug and hospitalization for heart failure. (DE 628-3, Goyal Report at 10; DE 710, Goyal Test. at 107.) Nevertheless, he stated in his report and testified that SAVOR's finding of a statistically significant increase in hospitalizations for heart failure after exposure to saxagliptin "should be interpreted as cause and effect unless there is compelling evidence to prove otherwise." (DE 628-3, Goyal Report at 8; DE 710, Goyal Test. at 67.)

This is contrary to reliable scientific method. First, "[r]arely, if ever, does a single study persuasively demonstrate a cause-effect relationship." Reference Manual on Scientific Evidence at 604. It is important that a study be replicated in different populations and by different investigators before a causal relationship is accepted by epidemiologists and other scientists. *Id*. "A good general rule of thumb in science is never to rely on any experimental

finding until it has been independently replicated." *Id*. at 777. Dr. Goyal agreed with all this at the hearing. (DE 710, Goyal Test. at 76-79.)[3]

Second, drawing "unauthorized conclusions from limited data – conclusions the authors of the study do not make" demonstrates a "lack of scientific rigor." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1248 (11th Cir. 2005); *see also In re Nexium Esomeprazole*, 662 F. App'x 528, 530 (9th Cir. 2016) (holding that expert was properly excluded when doctor "did not adequately explain how he inferred a causal relationship from epidemiological studies that did not come to such a conclusion themselves.") As discussed, the SAVOR authors themselves noted that "[t]here are presently no known mechanisms by which DPP-4 inhibition could precipitate heart failure." (DE 626-10, Scirica 2014 at 1585.) They cautioned that their observation of a higher incidence of hospitalization for heart failure among patients treated with saxagliptin "should be considered within the context of multiple testing that may have resulted in a false positive result." (DE 646-11, Scirica 2013 at 1324.) The authors specifically stated, "[t]his finding merits further investigation and needs to be confirmed in other ongoing studies, and a class effect should not be presumed." *Id*. In his rebuttal report, Dr. Goyal states that he "completely agree[s] with these points; and I would moreover argue that this [further investigation] is urgently needed." (DE 646-3, Goyal Rebuttal at 2.)

[3] In their post-hearing briefing, plaintiffs point out that, in a footnote, the Reference Manual on Scientific Evidence qualified that the requirement that a study be replicated before a causal relationship is established "may not be the legal standard." Reference Manual on Scientific Evidence at 604, n. 163. The single case cited for this proposition is a Western District of North Carolina district court case in which the court stated, in a footnote, that, consistency for purposes of the Bradford Hill analysis was difficult to establish because only one epidemiological study existed in that case. *Smith v. Wyeth-Ayerst Lab'ys Co*., 278 F. Supp. 2d 684, 710 (W.D.N.C. 2003). The court further noted that finding consistency was less important in that case because there was no real question as to general causation. Here, there are multiple studies on the issue of whether saxagliptin can cause heart failure and general causation is an issue. Thus, for a causation analysis, it is important to consider whether consistency among the various studies exists.

In his report, Dr. Goyal recognizes that multiple observational studies conducted after SAVOR have examined the association between saxagliptin and hospitalizations for heart failure. He does not consider them, however, in his analysis of whether an association between saxagliptin exposure and heart failure has been consistently reported in studies. He states that inferences from such studies "are generally limited due to issues related to confounding by indication and other residual unmeasured confounding issues." (DE 628-3, Goyal Report at 9.) Dr. Goyal never explains what specific confounding issues exist in each of the observational studies that he rejected or even explicitly states that the observational studies present any such issues. At the hearing, Dr. Goyal conceded that the observational studies were "reasonably designed." (DE 710, Tr. at 90.) He agreed that the observational studies collectively evaluated over 180,000 patients and that the number of patients was a strength of the studies. *Id*. at 91. Neither in his report nor at the hearing was Dr. Goyal able to identify any defects in any of the individual observational studies. *Id*. at 106.

Dr. Goyal conceded that no human study had ever confirmed the hospitalization-for-heart-failure finding in SAVOR. *Id*. at 44. He testified that he was aware that no other clinical trial or observational study confirmed the finding. *Id.* at 87, 91. Yet he failed to consider any of these studies in his causation analysis, and he provides no sound rationale for failing to do so. Failing "to adequately account for contrary evidence is not reliable or scientifically sound." *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prod. Liab. Litig*., 174 F. Supp. 3d 911, 932 (D.S.C. 2016).

Instead of considering any of the human data contained in the CVOTs other than SAVOR, the observational studies, or the meta-analyses, Dr. Goyal asserts in his report that "the best approach" to evaluate consistency is to review "pre-clinical studies to understand whether there were indicators of heart failure prior to SAVOR." (DE 628-3,

Goyal Report at 9.) The pre-clinical studies he discusses in his report involve only animal data. (DE 628-3, Goyal Report at 9-10.)

As discussed, however, according to the experts' testimony regarding the evidence "pyramid," animal studies are inferior evidence compared to observational studies. (Pfs.' Ex. 10.) Dr. Goyal agreed that, in analyzing studies, "the application of the evidence pyramid needs to be applied." (DE 710, Goyal Test. at 106.) He further agreed that animal studies are at the very bottom of the pyramid. (DE 710, Goyal Test. at 136.) He testified that he was not aware of any Bradford Hill analysis that had ever ignored available human data to determine consistency and had instead looked to animal data. (DE 710, Goyal Test. at 139.)

By failing to consider any of the relevant human data other than SAVOR without providing any sound rationale for failing to do so, Dr. Goyal violates Rule 702's requirement that his opinion be based on "sufficient facts or data." Fed. R. Evid. 702. Further, Dr. Goyal did not know if any of the animal studies he relied on were peer reviewed. (DE 710, Goyal Test. at 153.) And he conceded that he did not consider peer-reviewed animal studies that had findings inconsistent with a causal link between saxagliptin and heart failure. (DE 710, Goyal Test. at 153-56.)

As to the defendants' objections to Dr. Goyal's qualifications to interpret the animal data, it does not appear that, in any of the studies Dr. Goyal relies on, any animal was diagnosed with heart failure. Instead, Dr. Goyal undertook to determine himself whether any animals involved in the studies showed symptoms of heart failure. Dr. Goyal conceded at the hearing that none of the animal studies specified heart failure as an outcome or object of the study. (DE 710, Goyal Test. at 140-41.) Dr. Goyal relies on only certain isolated findings regarding the physical status of the animals and opines that these findings *could* be consistent with heart failure in the animals exposed to saxagliptin. For example, he states that, in one study, anemia and low albium were noted in an unspecified number of

both rodents and monkeys," which "*could* be suggestive of hemodilution, which is a marker of heart failure" and that, in another study, an unspecified number of rodents gained weight in the liver, spleen, and kidney which "*could* represent congestion . . . which is a hallmark of heart failure." (DE 628-3, Goyal Report at 9-10) (emphasis added). He finds "two overt cases of *apparent* cariogenic shock in monkeys." (DE 628-3, Goyal Report at 10) (emphasis added). One of the monkeys was determined by the researchers to have died of ileus, but Dr. Goyal finds that the monkey's symptoms "are highly suggestive of hypoperfusion that *could* be seen from a cardiac process." (DE 628-3, Goyal Report at 10) (emphasis added). As to the other monkey, Dr. Goyal determines that the monkey's symptoms indicate that "it is highly likely that a cardiac process was a major contributor in this case." (DE 628-3, Goyal Report at 10.)

Dr. Goyal conceded, however, that he has no expertise in diagnosing heart failure in animals. (DE 710, Goyal Test. at 141, 147.) He has never studied heart failure in animals. (DE 710, Goyal Test. at 147.) He conceded that he is not qualified to determine whether the animals in the studies he considered actually had heart failure. (DE 710, Goyal Test. at 148, 152.) Further, Dr. Goyal agreed that the animal studies regularly use "very large doses" and, thus, generate findings never seen in humans administered human doses. (DE 710, Goyal Test. at 162-63.) He testified that he did not know how to convert animal dosing to human dosing. (DE 710, Goyal Test. at 163.)

"Opinions based on animal studies have been rejected because of reservations about extrapolating from animals to humans or because the plaintiff's extrapolated dose was lower than the animals' – which is invariably the case because one would have to study unmanageable, gigantic numbers of animals to see results if animals were not given high doses." Reference Manual on Scientific Evidence at 23. Animal study results "must be extrapolated to another species – human beings – and differences in absorption,

metabolism, and other factors may result in interspecies variation in responses." *Id*. at 563. Another problem with animal studies is that "the high doses customarily used in animal studies require consideration of the dose-response relationship and whether a threshold no-effect dose exists. These matters are almost always fraught with considerable, and currently unresolvable, uncertainty." *Id*. Dr. Goyal has no expertise in these matters, which renders his findings from the animal studies unreliable.

Plaintiffs have attempted to downplay Dr. Goyal's reliance on the animal studies. In response to the motion to exclude, plaintiffs state that defendants "wholly overstate" the amount that Dr. Goyal relies on animal data for his analysis. They argue that "Dr. Goyal simply noted relevant preclinical data in his Bradford Hill analysis as potentially being supportive of the relevant factor." (DE 647, Response at 33.) At the hearing, Dr. Goyal testified that he simply thought "there were some interesting findings" in the animal studies and so he included those findings in his report. (DE 707, Goyal Test. at 196.) Plaintiffs argue in their post-hearing brief that Dr. Goyal did not "assign the animal studies much weight." (DE 721, Post-Hr'g Br. at 9.)

With the exception of studies regarding TZDs, however, the animal studies are the only studies other than SAVOR that Dr. Goyal mentions in his Bradford Hill analysis. As to the studies involving TZDs, Dr. Goyal considers studies involving this class of drugs for his analogy analysis but not studies involving DPP-4 inhibitors, the drug class to which saxagliptin belongs. He asserts that "saxagliptin differs from other agents in the DPP4 inhibitor class; so using other DPP4 inhibitors as an analogy would not suffice." (DE 628-3, Goyal Report at 14.) TZDs, however, are an entirely different class of diabetes drugs than saxagliptin and other DPP4 inhibitors.

For the analogy analysis, researchers look at analogous drugs to determine whether those drugs cause the same outcome. Dr Goyal chose TZDs as the analogous drug, not

because of any similarities between saxagliptin and TZDs, but because TZDs "can worsen heart failure; and thus provide[] an appropriate analogy." (DE 628-3, Goyal Report at 14.) In other words, Dr. Goyal cherry picked TZDs as a comparison only because they have been shown to cause the outcome at issue: worsened heart failure. "Result-driven analysis, or cherry-picking, undermines principles of the scientific method and is a quintessential example of applying methodologies (valid or otherwise) in an unreliable fashion." *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prod. Liab. Litig. (No II) MDL 2502*, 892 F.3d 624, 634 (4th Cir. 2018). "[C]ourts have consistently excluded expert testimony that 'cherry-picks' relevant data." *Id*. (quoting *EEOC v. Freeman*, 778 F.3d 463, 469 (4th Cir. 2015)). This is because such an approach "does not reflect scientific knowledge, is not derived by the scientific method, and is not 'good science.'" *Id*. (quoting *In re Bextra & Celebrex Mktg. Sales Practices & Prods. Liab. Litig.*, 524 F.Supp.2d 1166, 1176 (N.D. Cal. 2007)).

Another indication that Dr. Goyal's Bradford Hill analysis is not reliable is that he altered his opinion on several of the factors after writing his report. Regarding the specificity factor of the analysis, in his report, Dr. Goyal opined that the SAVOR hospitalization-for-heart-failure finding "provides some reasonable specificity for the causal link between saxagliptin and heart failure." (DE 628-3, Goyal Report at 11.) In his deposition, however, he testified that specificity was not met. (DE 710, Goyal Test. at 185.) And later, at the hearing, he testified that specificity is met if looking only to the "essence or the spirit of what specificity is about," but that the factor is not met under the "original 1965 Bradford Hill verbiage." (DE 710, Goyal Test. at 5, 125.) As to the biological-gradient factor, in his report, Dr. Goyal opined that the data "support a biological gradient." (DE 628-3, Goyal Report at 11.) But at the hearing, he testified that this factor is not met. (DE 710, Goyal Test. at 125.) And as to consistency, as discussed, Dr. Goyal opined in his report

that the "best approach remaining to evaluate consistency would be to review pre-clinical [animal] studies." (DE 628-3, Goyal Report at 9.) At the hearing, however, he analyzed consistency by looking at findings among various "subgroups" within the SAVOR study itself. (DE 710, Goyal Test. at 134-35.) In fact, as discussed, the plaintiffs now argue that Dr. Goyal did not really consider the animal studies at all.

Plaintiffs have not met their burden of showing by a preponderance of the evidence that 1) Dr. Goyal is qualified by knowledge, skill, experience, training, or education to interpret animal data in the manner he purports to or 2) that his testimony is reliable. Accordingly, the motion to exclude Dr. Goyal's testimony will be granted.

**III. Objections under Federal Rule of Evidence 403**

Plaintiffs also argue that each of the defendants' experts should be excluded as cumulative under Federal Rule of Evidence 403. The plaintiffs made clear after the hearing, however, that they will pursue these arguments closer to trial. Accordingly, the Court does not address those arguments here.

**IV. Conclusion**

For all these reasons, the Court hereby ORDERS as follows:

1) the defendants' motion to exclude the testimony of Dr. Parag Goyal (DE 626) is GRANTED;
2) the plaintiffs' motion to exclude the testimony of Dr. Suneil Koliwad (DE 630) is DENIED;
3) the plaintiffs' motion to exclude the testimony of Dr. Eric Adler (DE 633) is DENIED; and
4) the plaintiffs' motion to exclude the testimony of Dr. Todd Lee (DE 635) is DENIED.

This 5th day of January, 2022.

KAREN K. CALDWELL
UNITED STATES DISTRICT JUDGE
EASTERN DISTRICT OF KENTUCKY