UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF KENTUCKY
CENTRAL DIVISION
LEXINGTON

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

OPINION AND ORDER ON DEFENDANTS' MOTION FOR SUMMARY JUDGMENT (DE 746) AND PLAINTIFFS' MOTIONS TO MODIFY SCHEDULING ORDER (DE 748) AND TO FILE A SUPPLEMENTAL BRIEF (DE 757)

This matter is before the Court on the defendants' motion for summary judgment (DE 746).[1] Also before the Court are two motions by the plaintiffs. The first asks the Court to modify the scheduling order to permit plaintiffs time to identify a different general causation expert (DE 748). The second asks for leave to file a supplemental brief (DE 757) in opposition to the motion for summary judgment.

For the following reasons, the Court will grant the defendants' motion for summary judgment and the plaintiffs' motion to file a supplemental brief but will deny the plaintiffs' motion for more time to identify a general causation expert.

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 and Kombiglyze, both of which contain saxagliptin as an active ingredient. Onglyza is the brand

[1] All docket entry (DE) numbers refer to the docket entry numbers in the MDL Master File, 5:18-2809.

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. 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. 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*.

A. 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 CVOT for saxagliptin was called SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus). It was published in 2013. SAVOR 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, controlled 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 the 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 Prescribing Information provided to physicians 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%)." (DE 749-2, 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*.

B. 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.)

C. Post-SAVOR studies

As discussed, the SAVOR study tested for multiple endpoints, one of which was hospitalization for heart failure. 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 at *Daubert* hr'g; 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 at *Daubert* Hr'g, 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.)

D. Exclusion of Plaintiffs' only Expert on General Causation

In a complex medical case like this in which multiple plaintiffs allege injury from a pharmaceutical, "[c]ausation has two levels, general and specific, and a plaintiff must prove both." *Wells v. SmithKline Beecham Corp*., 601 F.3d 375, 378 (5th Cir. 2010). General causation addresses whether the pharmaceutical "is capable of causing a particular injury or condition in

the general population," while specific causation addresses whether the drug "caused a particular individual's injury." *Id*. (quoting *Knight v. Kirby Inland Marine Inc.*, 482 F.3d 347, 351 (5th Cir.2007)). "Sequence matters: a plaintiff must establish general causation before moving to specific causation. Without the predicate proof of general causation, the tort claim fails." *Id*.

In this action, the Court ordered that discovery would be conducted in two phases with the first phase addressing "'general causation,' i.e., whether saxagliptin is capable of causing any person to develop heart failure or other conditions alleged by the plaintiffs . . . . " (DE 179, Case Management Order No. 1.) Under Case Management Order No. 3 (DE 206), fact discovery on the issue of general causation was to be concluded by July 9, 2019. Expert discovery was to be concluded by September 27, 2019. Motions to exclude expert testimony under *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993) were to be fully briefed by December 20, 2019, with hearings to occur in January 2020. Those dates were extended multiple times. (DE 327, 437, 474, 529, 594.)

Ultimately, the plaintiffs identified one expert who opined that the available data establishes that saxagliptin is likely capable of causing heart failure: Dr. Parag Goyal. The plaintiffs also identified a second expert during the general causation phase of discovery: Martin Wells, PhD., a biostatistician. Plaintiffs have recognized that Dr. Wells "has no specialized training in heart failure and thus cannot opine on whether saxagliptin can cause heart failure. . . ." (DE 646, Response at 1, n.3.) As to the defendants, they identified five experts on general causation.

The plaintiffs moved to exclude the testimony and reports of four of the defendants' general causation experts. The defendants moved to exclude the testimony and reports of Dr. Goyal. They did not move to exclude Dr. Wells' testimony.

Beginning August 9, 2021, this Court and the Superior Court of California, which is presiding over the coordinated proceedings in California state court, conducted three days of joint hearings on the *Daubert* motions in Covington, Kentucky, after which the parties filed supplemental briefs. After the hearings, this Court entered an order granting the defendants' motion to exclude Dr. Goyal and denying the plaintiffs' motions to exclude the defendants' experts that were the subject of the *Daubert* hearings.[2]

As the Court more fully explained in its *Daubert* ruling, for his general causation opinion, Dr. Goyal relied on the SAVOR study to the exclusion of all other studies involving human data. He 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 recognized 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, Dr. Goyal stated in his report and testified at the *Daubert* hearing 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.)

"Rarely, if ever, does a single study persuasively demonstrate a cause-effect relationship." Federal Judicial Center, Reference Manual on Scientific Evidence 604 (3rd Ed. 2011). Further, 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,*

[2] The Court has not ruled on one of the plaintiffs' four motions to exclude the defendants' experts. Defense expert Dr. Michael Fowler was the subject of one of the motions to exclude but was not able to attend the *Daubert* hearings due to illness. Because the defendants are entitled to summary judgment, the Court will deny as moot the motion to exclude Dr. Fowler.

Inc., 401 F.3d 1233, 1248 (11th Cir. 2005). 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 stated that he "completely agree[d] with these points" and that he "would moreover argue that this [further investigation] is urgently needed." (DE 646-3, Goyal Rebuttal at 2.)

In his report, Dr. Goyal recognized that multiple observational studies conducted after SAVOR examined the association between saxagliptin and hospitalizations for heart failure. He did not consider them, however, in his analysis of whether an association between saxagliptin exposure and heart failure has been consistently reported in studies. (DE 628-3, Goyal Report at 9.) Dr. Goyal conceded that no human study had ever confirmed the hospitalization-for-heart-failure finding in SAVOR. (DE 710, Goyal Test. at 44.) He testified that he was aware that no other clinical trial or observational study confirmed the finding. *Id*. at 87, 91. Yet, Dr. Goyal failed to consider any of these studies in his causation analysis, and he provided no sound rationale for failing to do so. The Court excluded Dr. Goyal's opinion, finding that it was not based on "sufficient facts or data" as required by Federal Rule of Evidence 702 and that his methodology was contrary to reliable scientific method. (DE 740, *Daubert* Ruling at 30, 33.)

The defendants now move for summary judgment, arguing that the plaintiffs must have an expert on general causation in order to proceed to trial. The defendants also argue that the

plaintiffs' non-expert evidence is not sufficient evidence from which a reasonable juror could find that saxagliptin is capable of causing heart failure.

II. Analysis

A. The plaintiffs have not shown good cause to revise the scheduling order to permit them time to identify another general causation expert.

Three weeks after the defendants moved for summary judgment, plaintiffs moved to modify the scheduling order to permit them time to identify a new expert on general causation (DE 748). They further request that the Court stay ruling on the defendants' motion for summary judgment until the plaintiffs have disclosed the new expert and served a new report on the defendants, which would presumably moot the current summary judgment motion and beget a new round of expert discovery, *Daubert* briefing, another *Daubert* hearing, and, possibly, a new motion for summary judgment.

A scheduling order can be modified only for "good cause." Fed. R. Civ. P. 16(b)(4). Good cause exists when a deadline “cannot reasonably be met despite the diligence of the party seeking the extension.” Fed.R.Civ.P. 16 advisory committee's notes to 1983 amendment. “The primary measure of Rule 16’s ‘good cause’ standard is the moving party's diligence in attempting to meet the case management order's requirements.” *Inge v. Rock Fin. Grp.*, 281 F.3d 613, 625 (6th Cir. 2002) (quotation omitted). Another important measure under Rule 16’s good-cause standard is whether modification of the scheduling order would prejudice the nonmoving party. *Marcilis v. Township of Redford*, 693 F.3d 589, 597 (6th Cir. 2012).

The original deadline for the plaintiffs to serve expert reports was July 25, 2019, and expert discovery was to be completed by September 27, 2019. (DE 206, Case Management Order No. 3.) On the request of the parties, the Court extended those dates multiple times. (DE 327, 437, 474, 529, 594.) The latest deadline for the plaintiffs to serve expert reports was July

21, 2020. (DE 529, Case Management Order No. 9.) The plaintiffs ultimately identified Dr. Goyal as their only expert witness on general causation. This motion for yet more time to identify an expert witness comes more than two and a half years after the original deadline to serve expert reports and more than a year and a half after the most recent deadline to do so.

As to the plaintiffs' diligence in attempting to meet the Court's deadline for expert discovery, the plaintiffs *did* meet the deadline. They identified only Dr. Goyal. The parties then completed expert discovery and filed *Daubert* motions, which this Court has already heard and ruled upon. Thus, plaintiffs do not really request an *extension* of deadlines. They ask the Court to reopen expert discovery. They provide no reason, however, that they were unable to identify a reliable expert within the Court's most recent deadline.

As for their rationale, the plaintiffs argue the exclusion of Dr. Goyal was "unexpected." The Court issued its ruling excluding Dr. Goyal on January 5, 2022. The plaintiffs give no reason that they did not move to modify the scheduling order until nearly 11 weeks later and only after the defendants had spent time and money moving for summary judgment.

Further, the expectation that the Court would rule differently on the admissibility of an expert cannot constitute good cause for reopening expert discovery. "A litigant is never justified in assuming that the court has made up its mind until the court expresses itself to that effect, and a litigant's failure to buttress its position because of confidence in the strength of that position is always indulged in at the litigant's own risk." *Lujan v. Nat'l Wildlife Fed'n*, 497 U.S. 871, 897 (1990). The *Daubert* standard cannot be a surprise to any litigator. "Since *Daubert*, . . . parties relying on expert evidence have had notice of the exacting standards of reliability such evidence must meet." *Weisgram v. Marley Co.*, 528 U.S. 440, 455 (2000) (quotations omitted). "It is

implausible to suggest, post-*Daubert*, that parties will initially present less than their best expert evidence in the expectation of a second chance should their first try fail." *Id*.

As to prejudice, the parties spent significant resources conducting discovery, litigating multiple discovery disputes, briefing *Daubert* issues, and preparing for and attending consecutive days of hearings in Covington, Kentucky. The parties then spent more time and money on the summary judgment briefing. Plaintiffs now ask the Court to stay a ruling on the defendants' summary judgment motion and reopen expert discovery. They ask for an additional three months just to identify another expert. If the past history of this case is any indication, the additional expert discovery would likely involve significant additional time for multiple disputes with extensive briefing, which would be followed by another round of *Daubert* briefing and hearings and dispositive motions. This is unduly prejudicial to the defendants. There is nothing that distinguishes this case from any other where a party produces only one expert witness on a crucial issue who is later excluded. If reopening discovery to permit the party a second chance to identify an admissible expert were the appropriate relief here, then it would be appropriate in every such case.

Reopening discovery is especially unwarranted here because there is no evidence before the Court that the plaintiffs can locate another general causation expert. In his testimony at the *Daubert* hearings, Dr. Goyal was unable to identify any other expert who agreed with his opinion that it is more likely than not that saxagliptin is capable of causing heart failure. (DE 710, Goyal Test. at 68.) With this motion, the plaintiffs do not identify any such expert. Plaintiffs' counsel submits an affidavit stating that he has "communicated with multiple cardiologist experts" about the case. (DE 748-2, Clark Aff.) The Court does not doubt that. In fact, the Court assumes that plaintiffs' counsel began communicating with cardiologists since some time before 2016, when

they commenced filing these cases. (DE 1, Transfer Order.) Yet, in this motion filed in 2022, plaintiffs' counsel can only generally assure the Court that plaintiffs "can and will" produce an expert on general causation.

In their response brief to the motion to reopen discovery, the defendants pointed out this deficiency. Nevertheless, in their reply brief, the plaintiffs still do not identify an expert. Instead, they point to guidelines published in 2022 by the American Heart Association (AHA), the American College of Cardiology (ACC), and the Heart Failure Society of America (HFSA), which identify saxagliptin as a drug that "may worsen" heart failure. (DE 756, Reply at 3; DE 756-1, 2022 AHA Guidelines.) Plaintiffs state that the guidelines are evidence of a "general consensus" in the medical community that "saxagliptin is more likely than not capable of causing heart failure." (DE 756, Reply at 3.)

As the Court will explain more fully below, the warnings contained in the guidelines are based solely on the possible association between saxagliptin and hospitalizations for heart failure observed in the SAVOR study. The warnings are not based on any causation finding. Finding an association between two events is not the same as finding that one of the events likely caused the other. To establish a likely causation relationship, scientists face a much higher burden. (DE 631-3, Lee Report at 4.)

For example, in this case, each expert employed what is called the "Bradford Hill analysis" to determine if the available data indicates that saxagliptin is capable of causing 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 Court explained the Bradford Hill analysis in depth in its *Daubert* ruling and also addresses it in briefer form below. (DE 740, *Daubert* Ruling at 2-4.) For purposes of this motion to reopen discovery, the important point is that the AHA guidelines rely only on the association found in SAVOR. They do not rely on any further study or analysis establishing a causation relationship between saxagliptin and heart failure. Nor do the guidelines state that saxagliptin is likely capable of causing heart failure. Thus, the guidelines cannot constitute evidence of a "general consensus" in the medical community that "saxagliptin is more likely than not capable of causing heart failure" as plaintiffs assert. (DE 756, Reply at 3.)

And even if the guidelines did represent such a general consensus, the plaintiffs would need an expert to testify to that. The plaintiffs fail to identify any expert willing to do so. It would be unfair for the Court to halt these proceedings at this juncture based only on the possibility that the plaintiffs could find an acceptable general causation expert if granted yet more time to do so.

Finally, to the extent that plaintiffs indicate a belief that the Court erred in excluding Dr. Goyal, there is a remedy that is provided for in the normal course of litigation. That remedy is an appeal, not the reopening of discovery. Accordingly, the plaintiffs' motion to modify the scheduling order and hold the summary judgment motion in abeyance until the plaintiffs have identified a new general causation expert will be denied.

B. Defendants are entitled to summary judgment because the plaintiffs have failed to produce admissible expert testimony that saxagliptin is capable of causing heart failure.

Plaintiffs assert claims for strict liability (design defect and failure to warn) (Counts I and III); negligence (Count II); breach of warranty of merchantability (Count IV); breach of express warranty (Count V); breach of implied warranty (Count VI); violation of consumer protection

laws and deceptive trade practices (Count VII); loss of consortium (Count VIII); survival action (Count IX); and wrongful death (Count X). (DE 185 Master Complaint.)

There is no dispute that, to prevail on each of these claims, plaintiffs must prove causation. Defendants argue that, with the Court's exclusion of Dr. Goyal – the only expert identified by the plaintiffs to establish general causation – the plaintiffs' claims necessarily fail.

In response, the plaintiffs point out that, in a multidistrict litigation, the Court must apply the substantive state law of the transferor state. This is true. Defendants, however, have attached to their motion an appendix citing case law in all 50 states, the District of Columbia, the Virgin Islands, and Puerto Rico that requires the plaintiff in cases involving complex issues of medical causation to present expert testimony on the subject. (DE 746-2, 53-Jurisdiction Survey.) The Court has reviewed the case law and agrees with the defendants' assessment.

Other courts have also agreed. "While the specific language used by courts vary to some degree, all jurisdictions require expert testimony [to prove general causation] at least where the issues are medically complex and outside common knowledge and lay experience." *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prod. Liab. Litig.*, 227 F. Supp. 3d 452, 469 (D.S.C. 2017) (citing cases). *See also In re Mirena IUD Prod. Liab. Litig.*, 202 F. Supp. 3d 304, 310 (S.D.N.Y. 2016) (citation, footnote, and quotations omitted) ("[T]he substantive law across all relevant jurisdictions holds . . . that where a causal link is beyond the knowledge or expertise of a lay jury, expert testimony is required to establish causation."); *In re Baycol Prod. Litig*., 321 F. Supp. 2d 1118, 1126 (D. Minn. 2004) ("This Court joins with those courts that have held personal injury cases involving pharmaceuticals, toxins or medical devices involve complex questions of medical causation beyond the understanding of a lay person.") (citing cases).

Lay testimony may be acceptable to prove causation "in cases in which general experience and common sense will enable a layman to determine, with reasonable probability, the causal relationship between the event and the condition." *Baycol*, 321 F. Supp. 2d at 1125 (quoting *Dawson v. Briggs*, 107 S.W.3d 739, 753-54 (Tex. App. 2003)). For example, in a case involving a car wreck, "causation is fairly obvious – if one car collides with another, common sense dictates that a range of injuries from broken limbs to internal bleeding to death can result." *In re Meridia Prod. Liab. Litig.*, 328 F. Supp. 2d 791, 798 (N.D. Ohio 2004). However, "personal injury cases involving pharmaceuticals, toxins or medical devices involve complex questions of medical causation beyond the understanding of a lay person." *In re Baycol*, 321 F. Supp. 2d at 1126.

Expert testimony is necessary to prove general causation in such cases because "the injuries themselves are usually not immediately obvious and the connection between exposure and injury is not a matter of common sense or everyday experience." *Meridia*, 328 F. Supp. 2d at 798. Another complexity of causation in medical product liability cases is that "a variety of exposures frequently can associate with the" injury claimed by the plaintiffs. *Id*. For example, in *Meridia*, the issue was whether the anti-obesity drug Meridia was capable of causing cardiovascular injuries. Determining causation was made more complex because those taking Meridia were typically obese, "a condition that, alone, is a risk factor for cardiovascular disease." *Id*. In that kind of situation, expert testimony is necessary to establish that another condition, like exposure to a drug, could also cause the alleged injury.

This case involves such a situation. Patients prescribed saxagliptin have diabetes, which is a condition that, alone, is a risk factor for heart failure. (DE 626-27, Abraham Report at 5-6.) A Mayo Clinic case-control study reported that diabetic patients face more than double the risk of

heart failure. Another study showed that diabetic patients were 2.5 times more likely to develop heart failure than those without diabetes. Thus, when heart failure occurs among diabetic patients, expert testimony is necessary to establish that a factor other than diabetes, like saxagliptin, is also capable of causing heart failure. *Id*.

The plaintiffs do not identify even one state that does not require expert testimony to establish general causation in a complex medical case involving numerous plaintiffs like this one. The plaintiffs cite five cases on this issue, and they do not provide any in-depth explanation of how these cases are significant to this case. (DE 749, Response at 15, 17.) None of the cases supports the plaintiffs' argument that they need not produce expert medical testimony to create an issue of fact with regard to general causation in this case.

The first case cited by the plaintiffs, *Bostic v. Ga. Pacific Corp.*, 439 S.W.3d 332 (Tex. 2014), does not involve general causation. The issue was whether the plaintiffs presented sufficient evidence that exposure to asbestos caused a particular individual's death from mesothelioma. There was "no dispute that asbestos, when breathed into the lungs, *can* cause mesothelioma." *Id*. at 336 (emphasis added). The court explicitly stated, "In today's case, general causation is not an issue. Georgia-Pacific does not dispute, for purposes of this appeal, that exposure to asbestos fibers can cause mesothelioma." *Id*. at 348.

Plaintiffs cite *Bostic* for the proposition that, under Texas law, they can use "studies" to establish general causation. (DE 749, Response at 17.) In *Bostic*, the Texas Supreme Court explained that, in *Merrell Dow Pharms., Inc. v. Havner*, 953 S.W.2d 706, 720 (Tex. 1997), it had recognized a "quantitative approach to causation." *Bostic*, 439 S.W.3d at 347.

In *Havner*, the Texas court decided that,"where direct evidence of causation is lacking, scientifically reliable evidence in the form of epidemiological studies showing that the

defendant's product more than doubled the plaintiff's risk of injury appropriately corresponds to the legal standard of proof by a preponderance of the evidence." *Bostic.* 439 S.W.3d at 349-50. (citing *Havner*, 953 S.W.2d at 717-18)). In *Bostic*, the court further explained, however, that "[a] more than doubling of the risk must be shown *through reliable expert testimony* that is based on epidemiological studies or similarly reliable scientific testimony." *Id*. at 530 (emphasis added). Here, plaintiffs point to no studies that indicate that those diabetes patients who took saxagliptin faced more than double the risk of heart failure as compared to diabetes patients who did not take the drug. Nor have they produced an expert willing to so testify.

Plaintiffs also cite *Christian v. Gray*, 65 P.3d 591 (Okla. 2003). In that case, however, the Supreme Court of Oklahoma confirmed its prior holdings that, "[w]hen an injury is of a nature requiring a skilled and professional person to determine cause and the extent thereof, the scientific question presented must necessarily be determined by testimony of skilled and professional persons." *Id*. at 601–02. This is precisely the situation here.

The pivotal holding of *Christian* with regard to general causation was the court's agreement with the Kansas Supreme Court that "some cases are not appropriate for imposing a general causation requirement" at all. *Id.* at 603 (citing *Kuhn v. Sandoz Pharms. Corp*., 14 P.3d 1170 (Kan. 2000)). In *Kuhn*, the Kansas Supreme Court stated that the requirement to show general causation has typically been imposed in cases involving "mass exposure" and "large existing epidemiological records." *Christian,* 65 P.3d at 603 (quoting *Kuhn*, 14 P.3d at 1184-85). In contrast, in cases that involve a "sporadic accident" with only a single plaintiff or a few plaintiffs claiming injury from some exposure, the plaintiffs can prove causation through a medical doctor who renders an opinion based "solely on an examination of the plaintiff and a

differential diagnosis of the source of the plaintiff's injury, sometimes supplemented with toxicological evidence. . . ." *Christian,* 65 P.3d at 603 (quoting *Kuhn*, 14 P.3d at 1184-85.)

In *Christian*, the Oklahoma Supreme Court appears to have largely adopted the Kansas approach to general causation, concluding "that general causation should be shown unless the particular controversy is inappropriate for general causation." *Id*. at 604. While that holding may not be entirely instructive, the court declined to "list hypothetical controversies where general causation need not be shown." *Id*.

Plaintiffs in this case, however, have never argued that they should not be required to demonstrate general causation at all. Further, this is a case of mass exposure to a substance (saxagliptin). It is not a case involving a "sporadic accident" and a single or a few plaintiffs. Thus, even under *Kuhn* and *Christian*, plaintiffs must establish general causation. Regardless, neither *Kuhn* nor *Christian* hold that expert medical testimony is not necessary to prove general causation in a complex medical products liability action.

The next case plaintiffs cite seemingly for the proposition that they need not produce expert testimony to prove general causation is *Bailey v. N. Am. Refractories Co.*, 95 S.W.3d 868 (Ky. App. 2001). In that case, the plaintiffs alleged that exposure to asbestos caused them to suffer various illnesses. The plaintiffs here point out that the Kentucky Court of Appeals stated in *Bailey* that it was "well recognized that legal causation may be established by a quantum of circumstantial evidence from which a jury may reasonably infer that the product was a legal cause of the harm." *Id*. at 872-73 (quoting *Holbrook v. Rose*, 458 S.W.2d 155, 157 (1970)). However, in that case, the plaintiffs did present a medical expert on causation, and the court found that it was precisely the expert's testimony that created the sufficient "'quantum of circumstantial evidence' to raise a factual issue as to legal causation." *Id*. at 873. *Bailey* does not

support plaintiffs' argument that they need not produce an expert on general causation in this case.

Plaintiffs cite *Tousignant v. St. Louis City*, 615 N.W.2d 53 (Minn. 2000). They cite this case only for the proposition that "when the acts or omissions complained of are within the general knowledge and experience of lay persons, expert testimony is not necessary to establish a standard of care, even in cases of alleged medical malpractice." *Id*. at 58 (quotations and citation omitted). This makes sense and, as discussed, is consistent with the rule in the jurisdictions surveyed. In *Tousignant*, the court explained, however, that medical malpractice cases where expert testimony is not necessary are both "exceptional" and "rare." *Id*. (quoting *Sorenson v. St. Paul Ramsey Med. Ctr.*, 457 N.W.2d 188, 191 (Minn. 1990)). This is because "most medical malpractice cases involve complex issues of science or technology, requiring expert testimony to assist the jury in determining liability." *Id*. Whether saxagliptin is capable of causing heart failure in diabetes patients is not something that would be within the general knowledge and experience of laypersons. Thus, *Tousignant* does not support the plaintiffs' argument that they need not present an expert on general causation to survive summary judgment in this case.

Finally, the plaintiffs cite *Meridia* for the argument that they need not produce medical expert testimony on general causation. (DE 749, Response at 15.) In that case, however, the district court decided, "[r]ather than undertake an analysis of all fifty states' laws to determine which do and which do not require expert testimony on the issue of general causation," it would assume "that no states' laws erect such a requirement." 328 F. Supp. 2d at 802. The court explained it made no difference in that case because, either way, "the Court ends up in the same place: summary judgment for Defendants." *Id.*

Here, however, the Court *has* surveyed the law of all 50 states and the District of Columbia, Puerto Rico, and the Virgin Islands. The Court agrees with the defendants that all require expert testimony to establish general causation in a complex medical products liability case like this. Summary judgment for the defense is appropriate in such cases when the plaintiff cannot produce admissible expert testimony to show general causation. *Mirena IUD Prod. Liab. Litig.*, 202 F. Supp. 3d at 312 (citing cases). Because the plaintiffs have not produced admissible expert testimony that saxagliptin is capable of causing heart failure, the defendants' motion for summary judgment must be granted.

C. Even if expert testimony on general causation were not required, defendants are entitled to summary judgment because plaintiffs have produced no evidence from which a jury could fairly infer that saxagliptin is capable of causing heart failure.

Summary judgment is appropriate when the admissible evidence produced by the parties shows that "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). A genuine issue of material fact exists where "the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Anderson v. Liberty Lobby, Inc*, 477 U.S. 242, 248 (1986). In determining whether summary judgment is appropriate, the Court "must draw all justifiable inferences in favor of Plaintiffs as the non-moving party, and Plaintiffs' evidence is to be believed." *Gass v. Marriott Hotel Servs.*, 558 F.3d 419, 429 (6th Cir. 2009) (internal quotations, brackets, and citation omitted).

Thus, even if the Court were to assume, as the court did in *Meridia*, that the plaintiffs need not produce expert testimony on general causation to survive summary judgment, the plaintiffs nonetheless must point to sufficient other evidence from which a juror could reasonably infer that saxagliptin is capable of causing heart failure. The plaintiffs have failed to do so, and for this reason also, the Court must grant summary judgment to the defendants.

Most of the evidence of general causation that the plaintiffs cite deals only with the potential *association* between saxagliptin and heart failure observed in the SAVOR study. The plaintiffs cite the SAVOR study itself; warnings about saxagliptin based on the SAVOR study; and a draft of a 2013 white paper by an AstraZeneca statistician also based on SAVOR. (DE 749, Response at 15 & n.37, 16; DE 757-2, Supplemental Br. at 1.) The plaintiffs also cite the opinion of their expert, Dr. Wells. None of this is evidence from which a juror could fairly infer that saxagliptin is capable of *causing* heart failure.

1) The SAVOR study did not establish general causation.

In their response brief, the plaintiffs state that the SAVOR study alone established "that saxagliptin is capable of causing heart failure." (DE 749, Response at 4.) But the SAVOR study did not establish causation. The SAVOR authors do not state that the SAVOR study established causation. There is no expert remaining in this case who opines that this single study is evidence of causation. The plaintiffs' own expert, Dr. Wells, explained that the SAVOR study answered only whether there was an "association" between heart failure and saxagliptin not whether saxagliptin actually caused heart failure. (DE 707, Hr'g Tr. at 122, 124.) The SAVOR authors concluded only that "saxagliptin treatment was *associated* with an increased risk of hospitalization for heart failure." (DE 646-14, Scirica 2014 at 1) (emphasis added).

As discussed, the SAVOR authors cautioned that the observed 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." They advised that the observation needed confirmation through further studies. (DE 646-11, Scirica 2013 at 1324.) The SAVOR authors made similar statements in the 2014 follow-up study. (DE 626-10, Scirica 2014 at 1585.) While they stated that the observed increased risk of hospitalization for heart failure among saxagliptin

patients in the study was "likely valid," they continued to advise that the observation "must be taken in the context of multiple testing and the risk of a 'false-positive.'" They also explained that there were "no known mechanisms by which DPP-4 inhibition could precipitate heart failure." (DE 646-14, Scirica 2014 at 1585.)

No one in this case disputes that the heart failure events recorded in the SAVOR study actually occurred. (DE 712, Adler Test. at 27-28.) But, even if these events establish an *association* between saxagliptin and heart failure, that is a different thing than *causation*. Scientists must employ further analysis like the "Bradford Hill analysis" to determine if the available data indicates that there is actually a cause-effect relationship between two events.

The Bradford Hill 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.)

As explained more fully in the Court's *Daubert* ruling, in the case of saxagliptin and heart failure, the nine factors require scientists to look at issues like the strength of the association between the drug and heart failure; whether patients exposed to higher doses of the drug are more likely to develop heart failure or more severe heart failure; and whether a causation relationship is a biological possibility given what is known about human biology and heart failure. (DE 740, *Daubert* Ruling at 304.) Also among the nine factors is "consistency of

association." This factor asks whether the observed association has "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. (DE 628-3, Goyal Report at 9.)

Because the SAVOR study could not by itself establish that saxagliptin is capable of causing heart failure, each of the experts in this case employed the Bradford Hill causation analysis to make that determination. None of the remaining experts in this case opines that the SAVOR study alone could establish that saxagliptin is likely capable of causing heart failure. The plaintiffs point to no evidence from which any juror could fairly conclude that the SAVOR study itself establishes causation.

2) Warnings that are based on the SAVOR study cannot be evidence of general causation.

As evidence of causation, the plaintiffs also point to warnings about saxagliptin by the FDA and AHA that were based only on the SAVOR study. Just as the SAVOR study is not evidence of causation, neither are any warnings that are based only on the SAVOR study.

As to the FDA, Plaintiffs cite warnings contained in an April 5, 2016 FDA Drug Safety Communication (DE 749-3) and the resulting prescribing information and medication guide for saxagliptin (DE 749-2, Prescribing Information at CM-ECF pp. 2-31; DE 749-2, Medication Guide at CM-ECF pp. 32-34.)

As to the AHA, Plaintiffs cite warnings contained in the AHA's Aug. 9, 2016 Scientific Statement titled, "Drugs that May Cause or Exacerbate Hearth Failure" (DE 749-6) and, more recently, warnings contained in the April 1, 2022 publication discussed above by the AHA, the ACC, and the HFSA titled, "2022 AHA/ACC/HFSA Guidelines for the Management of Heart Failure." (DE 757-2, Supplemental Brief; DE 756-1, AHA 2022 Guidelines.)

The plaintiffs assert that the FDA and AHA issued these warnings because both entities "had concluded that saxagliptin was capable of causing heart failure based on the SAVOR results." (DE 749 at 7.) If the FDA and AHA had reached this conclusion based on SAVOR, the plaintiffs would need an expert to testify to that. The plaintiffs have pointed to no expert willing to do so. This is likely because neither the FDA nor the AHA expressed a conclusion that saxagliptin is capable of causing heart failure.

The warnings in the FDA and AHA publications are based only on the *association* between saxagliptin and hospitalization for heart failure that SAVOR may support. Neither the FDA nor the AHA conducted their own studies or causation analyses. Neither entity even purported to go further than the SAVOR authors themselves to state that saxagliptin is likely capable of causing heart failure.

The FDA's April 5, 2016 Drug Safety Communication explains that, as a result of the SAVOR study, the FDA has added warnings and precautions to the labels of medicines that contain saxagliptin. (DE 749-3, FDA Drug Safety Communication, at CM-ECF p. 3). Thus, the prescribing information issued by the defendants advises physicians to consider the risks of saxagliptin before prescribing it. (DE 749-2, Prescribing Information, § 5.2, Heart Failure at CM-ECF p. 4.) Likewise, the medication guide issued by the defendants advises

patients that, "[s]erious side effects can happen to people taking ONGLYZA, including. . . heart failure." (DE 749-2, Medication Guide at CM-ECF p. 32.)[3]

As to the AHA, its 2016 communication includes saxagliptin in a chart of "prescription medications that may cause or exacerbate" heart failure. (DE 749-6, AHA Statement at e34.) Like the FDA's warnings, this warning is based on the SAVOR findings. (DE 749-6, AHA Statement at e42.) More recently, the 2022 "Guidelines for the Management of Heart Failure" published by the AHA, the ACC, and the HFSA identify saxagliptin as a drug that "may cause or exacerbate" heart failure. (DE 756-1, 2022 AHA Guidelines, § 7.3.7, Table 13.) The guidelines recommend discontinuing saxagliptin in patients who develop heart failure (DE 756-1, 2022 AHA Guidelines at 45.) While published more recently, the guidelines with regard to saxagliptin are still based only on the SAVOR study. (DE 756-1, 2022 AHA Guidelines, § 7.3.7 at 45, 127 n. 22.)

Plaintiffs have not presented evidence or even argued that the FDA and AHA require proof of causation before issuing warnings. "It is widely recognized that, when evaluating pharmaceutical drugs, the FDA often uses a different standard than a court does to evaluate evidence of causation in a products liability action." *In re Neurontin Mktg., Sales Pracs., & Prod. Liab. Litig.*, 612 F. Supp. 2d 116, 136 (D. Mass. 2009).

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[3] Plaintiffs argue that, under *Meridia*, this statement in the saxagliptin Medication Guide should be deemed an admission by the defendants that saxagliptin is capable of causing heart failure. In *Meridia*, however, the product information contained a statement of causation. The information stated, "Meridia substantially increases blood pressure in some patients. . . ." 328 F. Supp. 2d at 810. The court found that statement to be an admission "of Meridia's potential to cause substantial increases in blood pressure in some patients." *Id*. The product information also listed conditions that were "associated" with Meridia. The court found those statements could not constitute admissions of causation. *Id*.

The saxagliptin medication guide contains a warning based only on the SAVOR study finding of, at most, an association between saxagliptin and heart failure. The guide states that heart failure "*can happen*" to people taking saxagliptin. This is not an affirmative statement that saxagliptin is capable of causing heart failure. It is not a statement of causation at all. Accordingly, it cannot be deemed to be an admission of causation.

> Entrusted with the responsibility of protecting the public from dangerous drugs, the FDA regularly relies on a risk-utility analysis, balancing the possible harm against the beneficial uses of a drug. Understandably, the agency may choose to "err on the side of caution," *Rider v.* [*Sandoz Pharms. Corp*., 295 F.3d 1194, 1201 (11th Cir. 2002)], and take regulatory action such as revising a product label or removing a drug from the marketplace "upon a lesser showing of harm to the public than the preponderance-of-the-evidence or more-like-than-not standard used to assess tort liability." *McClain v. Metabolife Int'l, Inc*., 401 F.3d 1233, 1250 (11th Cir.2005).

Id.

The FDA warnings and AHA guidelines might be based on the idea that, "[i]f a particular factor *might* cause a disease, and the factor is readily avoidable, why not advise the patient to avoid it?" *Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 673 (6th Cir. 2010). Such advice can be based on a single study showing an association between a drug and a disease. Neither that advice, nor the single study it is based on, however, can constitute evidence in the courtroom that the drug is likely capable of *causing* the disease.

3) Dr. Ycas's statement that a particular finding was *consistent* with a causation relationship is not evidence that saxagliptin is capable of causing heart failure.

Finally, the plaintiffs argue that a statement by AstraZeneca's principal statistician, Dr. J.W. Ycas, in a draft of a white paper dated 2013 constitutes evidence that saxagliptin is capable of causing heart failure. (DE 749, Response at 15-16.) Assuming that this draft paper would be admissible, it does not constitute evidence of causation.

The paper is titled, "Hospitalization for Heart Failure in SAVOR White Paper." Dr. Ycas "looked at some possible causal criteria to see whether they provide support, or tend to refute, the possibility that the [hospitalization for heart failure finding in SAVOR] represents a true causal relationship."

One of the criteria that Dr. Ycas looked at was the "relation of events to dosing of study drug." (DE 749-8, Ycas at CM-ECF p. 3.) He explains that, "[i]n true causal relationships, differentials in events often are seen closer to exposure, rather than far from the time of the last dose." (DE 749-8, Ycas at CM-ECF p. 3.) Dr. Ycas states that, "[i]n SAVOR, most [hospitalization for heart failure] was seen on-treatment or within 30 days after treatment." As plaintiffs point out, Dr. Ycas states, "While these small number of off-treatment cases are not conclusive, the observed pattern is consistent with a true causal effect, and not to chance variations during the off-treatment period." (DE 749-8, Ycas at CM-ECF p. 3.)

This is not an admission that saxagliptin is capable of causing heart failure. The statement deals with the results of just one of the causation criteria that Dr. Ycas studied – the events-to-dosing factor. He states the finding is "consistent with" causation. From this, he concludes, "the increased [hospitalization for heart failure rate] *may plausibly* represent a genuine causal effect and *needs to be further explored*." (DE 749-8, Ycas at CM-ECF p. 4) (emphasis added). As discussed, extensive studies after this 2013 draft white paper did not confirm a causal relationship. Regardless of those studies, however, a jury could not fairly infer from Dr. Ycas's statement in a draft paper regarding the events-to-dosing factor that saxagliptin is capable of causing heart failure.

4) Dr. Wells did not opine on general causation and is not qualified to do so.

As to Dr. Wells, he has explicitly stated that he did not opine on general causation in this case and that he is not qualified to do so. He is a biostatistician, a professor of statistical sciences at Cornell University and a professor of biostatistics and epidemiology at Cornell Weill Medical Center. (DE 707, Hr'g Tr. at 37; DE 747-4, Wells Report at 1.) He states in his report that he was asked only to "investigate the elevated risk of hospitalizations for heart failure from users of

saxagliptin within the SAVOR-TIMI-53 clinical trial" and to compare the "difference in effects size for hospitalization for heart failure in SAVOR and other randomized trials of DPP-4 inhibitors with a placebo comparator." (DE 749-4, Wells Report at 2.)

In his testimony at the *Daubert* hearing, Dr. Wells clarified that he was not asked to give a causation opinion. (DE 707, Hr'g Tr. at 45, 126-27.) Dr. Wells is not a physician. (DE 707, Hr'g Tr. at 118.) He explained that he was not asked to give a causation opinion because "heart failure is complicated" and he does not have the expertise or training to assess whether saxagliptin is capable of causing heart failure. (DE 707, Hr'g Tr. at 45.) He explicitly testified he is not qualified to opine on causality. (DE 707, Hr'g Tr. at 122, 148.) Moreover, in briefs, plaintiffs themselves have explicitly stated that "Dr. Wells has no specialized training in heart failure and thus cannot opine on whether saxagliptin can cause heart failure." (DE 647, Resp. at 1, n.3.)

Dr. Wells explained at the *Daubert* hearing that he performed the task he is qualified to perform: an analysis of SAVOR data to determine if there was an association between saxagliptin and heart failure. (DE 707, Hr'g Tr. at 122.) He explained that, "[y]ou need other expertise in order to reach the. . . causality conclusion." (DE 707, Hr'g Tr. at 122.)

Because the plaintiffs have not produced any admissible evidence that saxagliptin is capable of causing heart failure or any other injury, the Court must grant summary judgment to the defendants.

D. The defendants are not judicially estopped from disputing that saxagliptin is capable of causing heart failure.

Finally, the plaintiffs argue that, even if there is no evidence that saxagliptin can cause heart failure, the defendants are judicially estopped from disputing that such a causation relationship exists. The plaintiffs argue that the defendants have affirmatively represented to the

FDA that the SAVOR study "showed that saxagliptin may increase the risk of heart failure *and* Defendants agreed (in order to continue marketing and profiting from saxagliptin) to change their labels rather than remove saxagliptin from the market entirely." (DE 749, Response at 11.)

"Judicial estoppel forbids a party from taking a position inconsistent with one successfully and unequivocally asserted by that same party in an earlier proceeding." *Pennycuff v. Fentress Cnty. Bd. of Educ.*, 404 F.3d 447, 452 (6th Cir. 2005) (citation omitted). "Federal standards govern the application of judicial estoppel in federal court." *Id*. (citation omitted).

Under the doctrine of judicial estoppel, "[w]here a party assumes a certain position in a legal proceeding, and succeeds in maintaining that position, he may not thereafter, simply because his interests have changed, assume a contrary position, especially if it be to the prejudice of the party who has acquiesced in the position formerly taken by him." *New Hampshire v. Maine*, 532 U.S. 742, 749 (2001) (citation omitted). The purpose of the doctrine is to protect the integrity of the judicial process "by prohibiting parties from deliberately changing positions according to the exigencies of the moment." *Id*. (citation omitted).

In determining whether the doctrine applies, courts typically consider three factors:

1) whether a party's later position is "clearly inconsistent" with its earlier position;

2) whether the party has succeeded in persuading a court to accept that party's earlier position, so that judicial acceptance of an inconsistent position in a later proceeding would create the perception that either the first or the second court was misled; and

3) whether the party seeking to assert an inconsistent position would derive an unfair advantage or impose an unfair detriment on the opposing party if not estopped.

New Hampshire, 532 U.S. at 750–51.

Judicial estoppel applies only where the prior legal proceeding resulted in a "judicial or quasi-judicial endorsement" of the estopped parties' initial position. *Edwards v. Aetna Life Ins. Co.*, 690 F.2d 595, 600 (6th Cir. 1982). *See also In re Davol, Inc./C.R. Bard, Inc., Polypropylene Hernia Mesh Prod. Liab. Litig*., 546 F. Supp. 3d 679, 691 (S.D. Ohio 2021).

There are at least two problems with the plaintiffs' judicial estoppel argument. First, they have presented no evidence that the defendants' statements to the FDA were made in a judicial or quasi-judicial proceeding. Second, and more importantly, the statements are not inconsistent with the position that the defendants take in this litigation.

Plaintiffs assert that the statements by the defendants were made at an April 14, 2015 meeting of the FDA Endocrinologic and Metabolic Drugs Advisory Committee ("EMDAC"). (DE 749, Response at 13 & n.33.)

The purpose of the meeting was to "discuss the results of" the SAVOR trial. (DE 749-9, Meeting Tr. at 18, 21.) Representatives from the FDA and AstraZeneca presented. After each presentation, members of EMDAC asked questions. The EMDAC then conducted a public hearing, after which the members of the committee voted on two questions:

> 1) Based on information presented today and in background materials, do the results of SAVOR demonstrate that the use of saxagliptin in patients with type 2 diabetes has an acceptable cardiovascular risk profile?
>
> 2) Which action do you recommend [the] FDA take regarding the totality of the safety information, cardiovascular and other, obtained in SAVOR?

(DE 749-9, Meeting Tr. at 27, 143-68, 216-39.)

On question one, committee members were asked to vote, "yes," or "no." Thirteen committee members voted "yes." One member abstained. (DE 749-9, Meeting Tr. at 218.) The Acting Consumer Representative voted "no." (DE 749-9, Meeting Tr. at 224.)

On question two, committee members were asked to vote "A" (no change to the label), "B" (change label to add new safety information), "C" (change the label to add new safety information and restrict distribution), or "D" (withdraw saxagliptin from the market). (DE 749-9, Meeting Tr. at 228-29.) Fourteen members voted to change the saxagliptin label to add new safety information. The Acting Consumer Representative voted to withdraw saxagliptin from the market. (DE 749-9, Meeting Tr. at 228, 231.)

After the EMDAC meeting, the FDA issued the 2016 Drug Safety Communication discussed above, which stated that the FDA's safety review had found that medicines containing saxagliptin "may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. As a result, we are adding new warnings to the drug labels about this safety issue." (DE 749-3, FDA Drug Safety Communication, CM-ECF p. 1.)

Plaintiffs assert in a footnote (DE 749, Response at 12, n.30) that the EMDAC meeting and vote were "quasi-judicial" because they occurred under 21 U.S.C. § 355(o), which addresses postmarket studies, clinical trials, and labeling of new drugs. There is no evidence that the EMDAC meeting and vote occurred under this provision. The transcript of the EMDAC meeting never mentions this provision and Section 355(o) never mentions a meeting with an advisory committee or a vote. Section 355(o)(4)(A), the provision that the plaintiffs cite, discusses a notice from the FDA regarding changes in the label of a drug, a response by the drug manufacturer, a discussion period of up to 30 days (and longer if the FDA determines more time is warranted), followed by an order of the FDA and an appeal period. There is no evidence that any of this procedure occurred with regard to the EMDAC meeting and vote.

More importantly, even assuming that the EMDAC meeting and vote constituted a judicial or quasi-judicial proceeding for purposes of judicial estoppel, the doctrine nonetheless

cannot apply here because the defendants did not take a position at the meeting that is inconsistent with their position in this litigation.

Medical Doctors Howard Hutchinson, Jay Skyler, and Benjamin Scirica (the lead investigator for the SAVOR study), presented at the meeting on behalf of AstraZeneca. (DE 749-9, Meeting Tr. at 31-91.) In presenting the results of the SAVOR study, Dr. Scirica explained that "there was an increased risk of hospitalization for heart failure observed in the patients treated with saxagliptin." (DE 749-9, Meeting Tr. at 58.) Dr. Hutchinson explained, "SAVOR identified a new potential risk of hospitalizations for heart failure." (DE 749-9, Meeting Tr. at 76.) He stated, "We believe that the SAVOR study has established that there's the potential increased risk for hospitalization for heart failure. We think that needs to be treated like a real finding." (DE 749-9, Meeting Tr. at 88.) He further explained, however, that "the incremental risk for heart failure is low in comparison to the already high risk of heart failure in these patients." (DE 749-9, Meeting Tr. at 76.) He stated that AstraZeneca would "perform a study to evaluate potential mechanisms for this finding." (DE 749-9, Meeting Tr. at 77.)

That is not inconsistent with the defendants' position in this litigation. As discussed, there is no dispute that the hospitalizations for heart failure recorded in the SAVOR study actually occurred. (DE 712, Adler Test. at 27-28.) The issue here is their significance. No one at the EMDAC meeting testified that the SAVOR study established a causation relationship between saxagliptin and the recorded hospitalizations for heart failure.

Medical Doctor Mads F. Rasmussen, a member of EMDAC, summarized AstraZeneca's position at the 2015 EDMAC meeting as follows:

> I think the company has acknowledged that there is a potential risk, and they've initiated relevant activities to understand those better. Until we understand it better, the company has also proposed to include relevant safety information in the label to make sure that

> patients and prescribers can make that discussion amongst themselves to weigh-in that in the overall benefit-risk.

(DE 749-9, Meeting Tr. at 200.)

Medical Doctor Robert J. Smith, the chair of EMDAC, provided a similar summary, stating, "I think the voices of many people on the panel expressed concern about the observation of increased hospitalization for heart failure while acknowledging that the data are not definitive in firmly establishing that. . . ." (DE 749-9, Meeting Tr. at 200.)

At the time of the 2015 EMDAC meeting, the extensive additional testing discussed above regarding the relationship between saxagliptin and hospitalizations for heart failure had not taken place. After the SAVOR study and after the April 2015 EMDAC meeting, the multiple studies of the relationship between saxagliptin and heart failure were undertaken. As discussed, none of the observational studies found an association between saxagliptin and heart failure. (DE 635-10, Adler Report at 20; Defs.' *Daubert* Hr'g Ex. 10; DE 710, Goyal Test. at 87-88, 91, 99.) Likewise, the meta-analyses performed found no increased risk of heart failure among saxagliptin patients when the SAVOR data was excluded. (DE 630-3, Koliwad Report at 38; DE 626-27, Abraham Report at 31; Defs.' *Daubert* Hr'g Ex. 9, Iqbal 2014, Discussion.)

Thus, to the extent that the defendants' position is *different* in this litigation than it was at the 2015 EMDAC meeting, it is because the defendants have additional data now from which to determine if saxagliptin is capable of causing heart failure. Their position now is that the additional data does not establish that saxagliptin is capable of causing heart failure. This position is not *inconsistent* with their position before the EMDAC, at which the defendants 1) acknowledged a potential risk of heart failure among saxagliptin patients based solely on the SAVOR study, 2) indicated that additional testing was necessary regarding the relationship

between saxagliptin and heart failure, and 3) agreed to a warning label until the additional testing took place.

The defendants are not judicially estopped from arguing that the evidence does not establish a causation relationship between saxagliptin and heart failure.

III. Conclusion

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

1) Defendants' motion for summary judgment (DE 746) is GRANTED;
2) Plaintiffs' motion (DE 748) to modify the scheduling order and to stay ruling on this motion for summary judgment is DENIED;
3) Plaintiffs' motion to exclude the testimony of Dr. Michael Fowler (DE 630) is DENIED as moot;
4) Plaintiffs' motion for leave to file a supplemental response brief (DE 757) is GRANTED and the Clerk of the Court SHALL FILE in the record the tendered supplemental response brief (DE 757-2) and the tendered supplemental reply brief (DE 760-1);
5) Plaintiffs' motion for a hearing is DENIED, the Court finding that the parties have more than adequately briefed the motions currently before the Court and that a hearing is not necessary; and
6) Within 21 days of the entry date of this Opinion and Order, defendants SHALL FILE in this MDL Master File 5:18-2809 a list of all open cases that name defendants other than AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, and McKesson Corporation (the defendants who moved for summary judgment).

This 2nd day of August, 2022.

Karen K. Caldwell

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