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ONGLYZA PRODUCT CASES

A165387
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Synopsis

Background: Users of diabetes medications brought action against manufacturers and distributors of medications for personal injuries they allegedly suffered. The Superior Court, San Francisco City and County, No. CJC16004909, Anne-Christine Massullo, J., granted defendants' motion to exclude users' general causation expert, granted summary judgment in favor of defendants, and denied users' request to enlarge discovery deadlines to identify new causation expert. Users appealed.

Holdings: The Court of Appeal, Goldman, J., held that:

general causation opinion of proffered expert, who was cardiologist, was not based on reliable methodology, precluding its admission;

proffered expert opinion of biostatistician that data showed association between medication and significant increase in risk of hospitalization for heart failure was insufficient to raise triable issue as to causation;

whether a diabetes medication was capable of causing heart failure was required to be proven by expert testimony; and

trial court acted within its discretion in denying users' request to enlarge discovery deadlines to designate new causation expert.

Affirmed.

Trial Court: City and County of San Francisco Superior Court, Trial Judge: Honorable Anne-Christine Massullo (City & County of San Francisco Super. Ct. No. CJC16004909, JCCP No. 4909)

Attorneys and Law Firms

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Opinion

GOLDMAN, J.

***1** Plaintiffs Theodore Crites, Gary Gilmore, Ronald White, Yvonne Lyall, Lisa Hall, Mario Jimenez, Donald Leedy, Curtis Madden, Terry Miles, Paul Moore, John Okoye, Jose Ramos, Robert Rosencranse, and Barbara Thompson (collectively plaintiffs) appeal after the trial court granted the motion for summary judgment by defendants Bristol-Myers Squibb Company, AstraZeneca Pharmaceuticals LP (AstraZeneca), and McKesson Corporation (collectively defendants). Plaintiffs alleged injuries from saxagliptin, the main ingredient found in two medications manufactured and distributed by defendants to treat type 2 diabetes. The trial court first granted defendants' motion to exclude plaintiffs' general causation expert, who opined that saxagliptin can cause heart failure. Defendants then moved for summary judgment on the ground that, without expert testimony, plaintiffs could not show a triable issue of material fact as to general causation. The trial court agreed, and in the same order denied plaintiffs' request to enlarge discovery deadlines to allow them to identify a new causation expert. We affirm.

Background

A. SAVOR Study

In 2008, as part of defendants' application for approval of Onglyza and Kombiglyze XR, two diabetes drugs with saxagliptin as the active ingredient, the Endocrinologic and Metabolic Drugs

Advisory Committee of the Food and Drug Administration (FDA) required that defendant AstraZeneca perform a cardiovascular outcomes study to evaluate saxagliptin treatment in high-cardiovascular risk patients with type 2 diabetes. Known as SAVOR, it was a randomized, double-blind, placebo-controlled study that consisted of 16,492 patients with type 2 diabetes who were at high risk of cardiovascular disease.

SAVOR's "primary end point was a composite of cardiovascular death, myocardial infarction, or ischemic stroke." The study concluded that saxagliptin did not increase or decrease the risk of these occurrences. In addition, SAVOR examined various secondary end points that included hospitalization for heart failure, coronary revascularization, or unstable angina. Of the 10 secondary end points studied, the only statistically significant finding was for hospitalization for heart failure. The study concluded that "[m]ore patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8% ...)." The study's authors, however, noted that this finding "was unexpected and should be considered within the context of multiple testing that may have resulted in a false positive result." The authors further cautioned that the finding "merits further investigation and needs to be confirmed in other ongoing studies, and a class effect should not be presumed."

Following SAVOR, the FDA required that the labels for medications containing saxagliptin be updated to include a warning for the potential increased risk of heart failure. The warning label for Onglyza was updated to include text that SAVOR subjects "with a prior history of heart failure and subjects with renal impairment had a higher risk for hospitalization for heart failure, irrespective of treatment assignment." The label then stated, "[c]onsider the risks and benefits of ONGLYZA prior to initiating treatment in patients at a higher risk for heart failure." After the SAVOR finding, researchers conducted a number of observational studies of large groups of patients around the world to examine the risk of hospitalization for heart failure in users of saxagliptin as well as of other similar diabetes medications.[1] They did not find an association between saxagliptin and an increased risk of hospitalization for heart failure.

***2** Defendants' scientists also conducted a post hoc analysis of pooled data from 20 randomized controlled clinical trials of saxagliptin, and concluded that saxagliptin was not associated with an increased cardiovascular risk, including heart failure. As a possible explanation for SAVOR's different result, they noted that "SAVOR was an event-driven trial in a highly defined population (prior CV disease or multiple CV risk factors), whereas the 20 clinical trials analyzed in this study had defined treatment periods ranging from 4 to 206 weeks and included diverse patient populations with [type 2 diabetes] ...."

B. Lawsuits

Patients who took drugs with saxagliptin filed approximately 250 related cases in federal and state courts. Most of these cases were filed in federal court and consolidated into a federal multidistrict litigation (MDL) before the United States District Court for the Eastern District of Kentucky, with the rest filed in state courts in California and New York. The MDL court established a discovery plan in which the first phase would consist of discovery on general causation, including expert discovery and any *Daubert*[2] motions, and ordered the parties to coordinate discovery and other pretrial proceedings with the related state court cases to avoid duplication and inconsistency.

A Judicial Council coordination proceeding (JCCP) was established for the six state court cases filed in California, which later grew to include 13 cases. To conform as much as possible to the MDL's schedule, the court in the JCCP followed the MDL's discovery plan and ordered that the parties first conduct discovery on the issue of general causation, noting that litigation would proceed as to other issues only if plaintiffs were able to show general causation.[3]

During this first phase of discovery, plaintiffs designated two experts to support general causation, Dr. Parag Goyal and Dr. Martin Wells. Dr. Goyal is a cardiologist who was asked to opine whether saxagliptin was capable of causing heart failure. Answering the question affirmatively, Dr. Goyal relied on SAVOR's finding of an increased risk of hospitalization for heart failure. He also supported his conclusion with a Bradford Hill analysis, a widely-used methodology to evaluate whether a causal inference can be drawn from epidemiological studies. The analysis examines nine factors: strength, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experiment, and analogy. (Green et al., *Reference Guide on Epidemiology*, in Reference Manual on Scientific Evidence (3d ed. 2011) 549, 600 (*Reference Guide*).)

Dr. Wells is a biostatistician who performed an analysis of SAVOR data as well as meta-analyses applying SAVOR data. He concluded that the SAVOR data showed "a significant increase in the risk of hospitalization for heart failure in the saxagliptin arm in SAVOR at various time points throughout duration of the study." He further concluded that the meta-analyses "strongly support that saxagliptin has a distinct risk for hospitalization for heart failure profile than the other DPP-4 inhibitor drugs compared." Dr. Goyal relied in part on Dr. Wells' statistical analyses in forming his opinions.

***3** Defendants designated five experts who all opined that there was insufficient evidence to demonstrate a causal relationship between saxagliptin and heart failure.

C. Motion to Exclude Dr. Goyal's Testimony

Following expert discovery, defendants moved to exclude Dr. Goyal's testimony. They argued that Dr. Goyal (1) unreliably found causation based on the SAVOR study alone while disregarding other human data, including other clinical trials and the observational studies; (2) analyzed animal data even though he was unqualified to do so; and (3) misapplied each of the nine factors of the Bradford Hill analysis. A joint *Daubert*/*Sargon*[4] hearing took place in the JCCP and MDL. Dr. Goyal and Dr. Wells both testified at the hearing regarding their backgrounds, methodologies used, and the opinions they formed. The court also heard the testimony of three of defendants' five causation experts.

Following the hearing, the trial court granted defendants' motion.[5] First, the court held that any "opinions regarding the inferences relevant to the Bradford Hill analysis that may be drawn from the animal studies went beyond [Dr. Goyal's] expertise and were not supported by a reliable methodology." Second, the court found unreliable Dr. Goyal's opinion that the SAVOR finding alone supports causation, as "epidemiological studies can demonstrate only association, not causation." The court also explained why Dr. Goyal's application of most of the nine Bradford Hill factors was unreliable and inadmissible. For example, the "consistency" factor looks at whether similar findings are generated across multiple epidemiological studies. In analyzing this factor, Dr. Goyal dismissed certain human studies and testified that this factor could be established through SAVOR alone since SAVOR included multiple groups of patients in different settings. In sum, the court concluded that "Dr. Goyal's opinion does not contain a reliable methodology for weighing the evidence but a shifting results-based methodology that fails to logically and consistently weigh all relevant evidence."

D. Motion for Summary Judgment

Defendants then moved for summary judgment on the ground that, without any expert testimony on general causation, plaintiffs were unable to show a triable issue of material fact on that issue. In their opposition, plaintiffs argued that even without Dr. Goyal's opinion, there was sufficient evidence to create a triable issue of fact as to whether saxagliptin can cause heart failure. They pointed to the expert report of Dr. Wells, defendants' updated saxagliptin label that included a heart failure warning, and a warning issued by the American Heart Association (AHA) that saxagliptin could cause heart failure. In the alternative, plaintiffs requested that the court allow more time for plaintiffs to substitute another expert in place of Dr. Goyal.

***4** The trial court granted defendants' motion and denied plaintiffs' request to designate a new expert. The court held that summary judgment was proper "because Plaintiffs' claims rely on general causation, general causation requires expert testimony, and Plaintiffs are unable to present expert testimony on general causation." The court held that Dr. Wells' testimony was insufficient to support a finding of general causation because he was unqualified to provide an

ultimate opinion that saxagliptin can cause heart failure.

Plaintiffs now appeal.[6]

Discussion

A. Standard of Review

Summary judgment is proper "if all the papers submitted show that there is no triable issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." (Code Civ. Proc., § 437c, subd. (c).) A defendant seeking summary judgment "bears the burden of persuasion that there is no triable issue of material fact and that he is entitled to judgment as a matter of law." (*Aguilar v. Atlantic Richfield Co.* (2001) 25 Cal.4th 826, 850, 107 Cal.Rptr.2d 841, 24 P.3d 493.) A defendant meets this burden by showing that the plaintiff "has not established, and cannot reasonably expect to establish" an essential element of his claim. (*Saelzler v. Advanced Group 400* (2001) 25 Cal.4th 763, 768, 107 Cal.Rptr.2d 617, 23 P.3d 1143.)

We review a grant of summary judgment de novo, which means we "decide independently whether the facts not subject to triable dispute warrant judgment for the moving party as a matter of law." (*Intel Corp. v. Hamidi* (2003) 30 Cal.4th 1342, 1348, 1 Cal.Rptr.3d 32, 71 P.3d 296.) In deciding whether a material issue of fact exists for trial, we "consider all of the evidence set forth in the papers, except the evidence to which objections have been made and sustained by the court, and all inferences reasonably deducible from the evidence." (Code Civ. Proc., § 437c, subd. (c).) We view the evidence in the light most favorable to the plaintiff, as the nonmoving party. (*Saelzler v. Advanced Group 400*, *supra*, 25 Cal.4th at p. 768, 107 Cal.Rptr.2d 617, 23 P.3d 1143.)

On the other hand, a trial court's ruling excluding or admitting expert testimony is generally reviewed for abuse of discretion. (*Sargon, supra*, 55 Cal.4th at p. 773, 149 Cal.Rptr.3d 614, 288 P.3d 1237.) "A ruling that constitutes an abuse of discretion has been described as one that is 'so irrational or arbitrary that no reasonable person could agree with it.' [Citation.] But the court's discretion is not unlimited.... Rather, it must be exercised within the confines of the applicable legal principles." (*Ibid.*)

B. Applicable Legal Principles

Trial courts have a "substantial 'gatekeeping' responsibility" in excluding unreliable expert testimony. (*Sargon, supra,* 55 Cal.4th at p. 769, 149 Cal.Rptr.3d 614, 288 P.3d 1237.) This is to "ensure that an expert's opinion is based on both reliable material and sound reasoning." (*Bader v. Johnson & Johnson* (2022) 86 Cal.App.5th 1094, 1104, 303 Cal.Rptr.3d 162.)

Evidence Code [7] section 801 limits expert testimony to opinions that are "[r]elated to a subject that is sufficiently beyond common experience that the opinion of an expert would assist the trier of fact" and "[b]ased on matter ... that is of a type that reasonably may be relied upon by an expert in forming an opinion upon the subject to which his testimony relates." (§ 801, subds. (a) & (b).) Section 802 states that a witness, including an expert, may "state on direct examination the reasons for his opinion and the matter ... upon which it is based, unless he is precluded by law from using such reasons or matter as a basis for his opinion." In sum, "Evidence Code section 801 governs judicial review of the *type* of matter; Evidence Code section 802 governs judicial review of the *reasons* for the opinion." (*Sargon, supra,* 55 Cal.4th at p. 771, 149 Cal.Rptr.3d 614, 288 P.3d 1237.)

***5** However, "whether the expert opinion is founded on sound logic is not a decision on its persuasiveness. The court must not weigh an opinion's probative value or substitute its own opinion for the expert's opinion. Rather, the court must simply determine whether the matter relied on can provide a reasonable basis for the opinion or whether that opinion is based on a leap of logic or conjecture. The court does not resolve scientific controversies. Rather, it conducts a 'circumscribed inquiry' to 'determine whether, as a matter of logic, the studies and other information cited by experts adequately support the conclusion that the expert's general theory or technique is valid.' [Citation.] The goal of trial court gatekeeping is simply to exclude 'clearly invalid and unreliable' expert opinion." (*Sargon, supra,* 55 Cal.4th at p. 772, 149 Cal.Rptr.3d 614, 288 P.3d 1237.) As the high court noted, the focus of the trial court's inquiry "must be solely on principles and methodology, not on the conclusions that they generate." (*Daubert v. Merrell Dow Pharmaceuticals, Inc., supra,* 509 U.S. at p. 595, 113 S.Ct. 2786.)

C. The Trial Court Did Not Abuse its Discretion in Excluding Dr. Goyal's Testimony

With those general principles in mind, we now turn to the merits. Plaintiffs contend that the trial court exceeded its gatekeeping responsibility in excluding Dr. Goyal's opinions. Plaintiffs' primary argument is that, under the principles set forth in *Sargon, supra,* 55 Cal.4th 747, 149 Cal.Rptr.3d 614, 288 P.3d 1237, Dr. Goyal was permitted to place more weight on certain evidence, like SAVOR, and less weight on other evidence, like the human observational studies. They contend that the trial court could not properly exclude Dr. Goyal's testimony on this basis.

While we agree that the trial court may not weigh an expert opinion's probative value or persuasiveness, it must still consider whether the opinion is logically sound. (*Sargon, supra*, 55 Cal.4th at p. 772, 149 Cal.Rptr.3d 614, 288 P.3d 1237.) Here, the trial court explained in its detailed exclusion order that "Dr. Goyal's opinion does not contain a reliable methodology for weighing the evidence but a shifting results-based methodology that fails to logically and consistently weigh all relevant evidence." We find no abuse of discretion.

First, with respect to SAVOR, plaintiffs argue that Dr. Goyal was permitted to place the most weight on this study because randomized controlled trials "are the gold standard of evidence-based medicine ..." However, in his expert report, Dr. Goyal went one step further and concluded that the finding from SAVOR *alone* showed a causal link between saxagliptin and heart failure. The trial court noted that "epidemiological studies can demonstrate only association, not causation." Indeed, "[r]arely, if ever, does a single study persuasively demonstrate a cause-effect relationship. 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." (*Reference Guide, supra*, at p. 604.) This does not go to the weight of the evidence, but rather to the reliability of Dr. Goyal's methodology in basing his opinion on a *type* of matter that, by itself, does not show causation.

Plaintiffs argue that "the law is clear that an expert does not have to base their opinion upon any specific type of epidemiological evidence to reliably opine that a drug caused an injury." They cite *Davis v. Honeywell Internat. Inc.* (2016) 245 Cal.App.4th 477, 199 Cal.Rptr.3d 583, but that case merely held that, in addition to epidemiological studies, which the court agreed provided the best evidence of causation in most instances, an expert may also rely on other evidence such as case series reports, especially if the subject medical condition or health outcome is very rare. (*Id.* at p. 491, 199 Cal.Rptr.3d 583.) The court in any case found that the plaintiff's expert reviewed at least three epidemiological studies to support his opinion that the plaintiff's exposure to asbestos contributed to his development of mesothelioma. (*Id.* at pp. 489-490, 199 Cal.Rptr.3d 583.)

***6** A trial court does not abuse its discretion in excluding expert testimony on general causation when the expert's opinion is based on a single study that provides no reasonable basis for the opinion offered. (*Lockheed Litigation Cases* (2004) 115 Cal.App.4th 558, 564–565, 10 Cal.Rptr.3d 34.) Here, SAVOR's own authors stated that the finding of increased hospitalization for heart failure among saxagliptin users "was unexpected and should be considered in the context of multiple testing that may have resulted in a false positive result" and "needs to be confirmed in other ongoing studies ...." They therefore rejected the notion that the SAVOR study alone established a causal link.[8] In his rebuttal report, Dr. Goyal *agreed* that reproducibility of SAVOR's finding was important for determining causation and that replication of the finding was "urgently needed," but stated that there has been "no additional peer-reviewed data on this" since SAVOR. At the hearing, Dr. Goyal agreed that consistency in findings was an important factor in determining causation, that any experimental finding should

not be relied upon until it has been independently replicated, and that SAVOR's finding of increased heart failure could have been chance. We do not hold that one randomized controlled trial is never sufficient to establish general causation, but on this record, the trial court did not abuse its discretion in finding that Dr. Goyal's reliance on SAVOR alone to establish general causation was logically unsound, especially given Dr. Goyal's own agreement that SAVOR's finding needed to be replicated in order to determine causation.

Second, plaintiffs argue that Dr. Goyal reliably performed the Bradford Hill analysis, an accepted methodology that was also used by defendants' own experts. They again argue that the trial court improperly excluded Dr. Goyal's opinions based on the *weight* he placed on certain evidence under this analysis. The court's order, however, explained that its decision was based on various methodological defects it found in Dr. Goyal's application of six of the nine Bradford Hill factors, and that because he failed to weigh them together, it could not identify any predicate opinion on a specific factor that was not essential to his ultimate opinion. As a result, it concluded that methodological defects in any of the factors would upset the ultimate opinion on causation. This was a proper exercise of the court's gatekeeping responsibility. We discuss Dr. Goyal's application of some of these factors below.

"Strength of association" examines how strong the association is between the exposure and the disease. "The higher the relative risk, the greater the likelihood that the relationship is causal. For cigarette smoking, for example, the estimated relative risk for lung cancer is very high, about ten." (*Reference Guide*, *supra*, at p. 602.) Here, SAVOR found the hazard ratio for hospitalization for increased heart failure to be 1.27. Although Dr. Goyal opined that SAVOR was a reliable study for assessing strength, his report did not conclude whether a 1.27 hazard ratio reflected a strong or weak association. When asked about this factor at his deposition, Dr. Goyal could not say whether 1.27 was a strong association and testified that the word "strong" was too subjective for him to interpret. The trial court therefore found that Dr. Goyal had not actually given an opinion as to strength and that he was "refusing to engage with a factor of the Bradford Hill analysis on its terms."

"Consistency," as Dr. Goyal's own report explains, "is upheld when the same finding is shown in multiple studies across different populations and settings."[9] On this factor, Dr. Goyal disregarded inconsistent data from other human studies and relied on data from preclinical animal studies, opining that this was "the best approach" for evaluating consistency. The trial court noted, however, that Dr. Goyal conceded that he was not qualified to interpret animal data, and that the animal studies had the same defect Dr. Goyal cited to justify disregarding the human studies—namely, that cardiovascular safety was not a primary focus. Moreover, at the *Daubert*/*Sargon* hearing, Dr. Goyal offered a new and different opinion from the one in his report, contending that consistency was met through the SAVOR study alone since SAVOR looked at different populations across 16,000 patients. The trial court again concluded that Dr. Goyal did not apply the "consistency" factor on its own terms, since it requires the same finding across *different* studies with different researchers using different methodologies. This conclusion

was not based on the weight Dr. Goyal assigned to different evidence, but the unreliability of his shifting, results-based methodology.

***7** "Specificity" is met "if the exposure is associated only with a single disease or type of disease." (*Reference Guide, supra,* at p. 604.) Or, as Dr. Goyal explained, "only one cause should be leading to a single effect." His report stated this factor was supported because SAVOR was "a large, prospective, 'gold standard' RCT, designed in part to assess an association between saxagliptin and hospitalization for heart failure." At his deposition, when asked whether the specificity criterion was met, Dr. Goyal responded no. At the hearing, Dr. Goyal testified that "as much as we now know about science and medicine, you know, there's very few things where one cause actually only has a single effect." He then testified that specificity was nonetheless met through SAVOR because "the randomized controlled trial allows you to fulfill that criterion." Similar to his "strength of association" analysis, the trial court criticized Dr. Goyal's redefinition of this factor and his analysis as "another example of Dr. Goyal refusing to engage with a factor of the Bradford Hill analysis on its terms."

As stated in Dr. Goyal's report, "[b]iological gradient refers to a dose-response relationship between the exposure and outcome," or in other words, whether greater amounts of the putative cause are associated with increases in the occurrence of the disease or harm. The report cited data from the pre-clinical animal studies to support this factor, but the trial court held that Dr. Goyal could not offer this opinion because, as discussed above, he was unqualified to interpret animal data. At the *Daubert/Sargon* hearing, he instead testified that there was an absence of data as to this factor and that it was "hard to say in either direction." The trial court observed that the change in Dr. Goyal's opinions between the time of his report and the hearing underscored its concerns about their reliability, but it found admissible his opinion that there was insufficient human data to evaluate this factor.

Biological plausibility refers to whether there is a plausible biological mechanism to explain a cause and effect relationship between exposure and disease. The report stated there were "multiple published, proposed biological mechanisms." The trial court noted that the strongest mechanism Dr. Goyal could identify was only "a proposed hypothesis." Plaintiffs contend that "the trial court improperly held him to a higher standard than *Sargon* requires because he does not have to prove the mechanism with certainty to opine as to biological plausibility." But the court did not exclude Dr. Goyal's opinions due to a lack of certainty; it found that he did "not undertake an analysis of whether the data that exists supports or undermines his opinion that the proposed mechanisms are plausible," and conceded that data from cardiovascular outcome trials weighed *against* his underlying premise that hospitalization for heart failure was "a class-wide effect" across all DPP-4 inhibitors. As a result, the trial court found Dr. Goyal's opinion to be unreliable.

"Analogy" considers whether there have been associations found between a related or similar substance to the one at issue and the disease or outcome. With respect to saxagliptin and heart

failure, Dr. Goyal contended it was most relevant to examine "known links between other anti-diabetes drugs and heart failure." A number of human observational studies conducted after SAVOR found no association between increased hospitalization for heart failure and DPP-4 inhibitors. Dr. Goyal, however, stated that it would not suffice to use other DPP-4 inhibitors as an analogy because "saxagliptin differs from other agents in the DPP-4 inhibitor class." Instead, Dr. Goyal analogized saxagliptin to thiazolidinediones (TZDs), a different class of diabetes medications that has been linked to an increased risk of heart failure. However, he conceded that, while they have some similarities, TZDs and DPP-4 inhibitors differ in many ways and do not address or treat diabetes in the same way. The trial court reasonably concluded that this opinion was not reliable because the only reason for Dr. Goyal to analogize saxagliptin to TZDs rather than to other DPP-4 inhibitors was that the former supported his ultimate conclusion on causation and the latter did not.

***8** The trial court did not exceed its gatekeeping authority in concluding that Dr. Goyal's opinions were unreliable and inadmissible. Again, it was not the weight afforded to certain evidence that the trial court found problematic, but the shifting and unsound methodology Dr. Goyal utilized in weighing the evidence. For example, in order to opine that "strength" and "specificity" were satisfied, Dr. Goyal did not engage with these factors on their own terms, but redefined their meanings so that SAVOR's finding could support his conclusions. As already discussed, SAVOR's finding alone does not support general causation.

In *Lockheed Litigation Cases, supra,* 115 Cal.App.4th 558, 10 Cal.Rptr.3d 34, the court explained that though the expert relied on an epidemiological study, the study itself "must provide a reasonable basis for the particular opinion offered, and ... an expert opinion based on speculation or conjecture is inadmissible." (*Id.* at p. 564, 10 Cal.Rptr.3d 34.) There, the plaintiffs alleged that their occupational exposure to five chemicals manufactured and supplied by the defendants caused personal injuries. (*Id.* at pp. 561, 565, 10 Cal.Rptr.3d 34.) Plaintiffs' expert relied on a single study to find causation, but the study itself reviewed the association between painters' exposure to more than 130 different chemicals and the increased risk of cancer. (*Id*. at p. 564, 10 Cal.Rptr.3d 34.) Because the study provided no reasonable basis for the expert opinion that the five specific chemicals to which the plaintiffs were exposed caused an increased risk of cancer, the court found that the trial court's exclusion of the plaintiffs' expert was not an abuse of discretion. (*Id*. at p. 565, 10 Cal.Rptr.3d 34.) Here, for different reasons, the trial court also found Dr. Goyal's reliance on the SAVOR study to be unsound and his application of the Bradford Hill factors to be unreliable.

In *San Francisco Print Media Co. v. The Hearst Corp.* (2020) 44 Cal.App.5th 952, 258 Cal.Rptr.3d 180, our colleagues in Division Three emphasized that, when exercising its gatekeeping role, the trial court does not weigh an expert opinion's persuasiveness but instead "must focus on principles and methodology to determine whether the opinion is founded on sound logic ...." (*Id.* at p. 962, 258 Cal.Rptr.3d 180.) There, the court found no abuse of discretion in the trial court's exclusion of the plaintiff's expert because his analysis and

methodology "suffered from a clear foundational problem" and was "not the mark of an opinion rooted in sound logic." (*Id.* at p. 963, 258 Cal.Rptr.3d 180.) Likewise, here, the trial court found serious flaws in Dr. Goyal's methodology where he "failed to engage in a candid weighing of the evidence, choosing instead to avoid mentioning facts or entertaining conclusions that weighed against an ultimate conclusion of general causation." This methodology resulted in an unsound and unreliable opinion.

In sum, we conclude that, in evaluating Dr. Goyal's application of the Bradford Hill criteria, the trial court did not impermissibly weigh the evidence but considered whether Dr. Goyal's methodology was reliable.

D. Summary Judgment Was Properly Granted

1. Dr. Wells' Expert Testimony is Insufficient to Create a Triable Issue

Plaintiffs next argue that, even without Dr. Goyal's testimony, the unchallenged testimony of their second expert, Dr. Wells, was sufficient to raise a triable issue of fact as to general causation. Dr. Wells is a biostatistician who performed an analysis of SAVOR data and meta-analyses applying SAVOR data that Dr. Goyal relied on in part in forming his opinions as to general causation. Though Dr. Wells concluded that data from SAVOR showed an *association* between saxagliptin and "a significant increase in the risk of hospitalization for heart failure," he testified that he was not asked to provide an opinion as to medical causation because "[h]eart failure is complicated" and doctors are the ones who have the training and expertise to make that assessment, not him. Dr. Wells later reiterated that he was not qualified to provide an opinion as to general causation.

***9** As a heart failure cardiologist, whether saxagliptin was capable of causing heart failure was within Dr. Goyal's area of expertise, and plaintiffs tasked him with examining all the evidence, including Dr. Wells' statistical analyses, to determine whether the association between saxagliptin and increased heart failure reflected causation under the Bradford Hill factors. We therefore find that Dr. Wells' testimony alone does not create a triable issue of fact as to general causation.

2. Plaintiffs' Non-Expert Evidence is Insufficient to Create a Triable Issue

In addition to Dr. Wells' testimony, plaintiffs contend that there is other non-expert evidence showing saxagliptin is capable of causing heart failure that is sufficient to withstand a motion for summary judgment. We disagree.

First, "[t]he law is well settled that in a personal injury action causation must be proven within a reasonable medical probability based upon competent expert testimony." (*Jones v. Ortho Pharmaceutical Corp.* (1985) 163 Cal.App.3d 396, 402, 209 Cal.Rptr. 456 (*Jones*).) This is especially true when the cause of a disease or harm "is beyond the experience of laymen and can only be explained through expert testimony." (*Id.* at p. 403, 209 Cal.Rptr. 456.) Summary judgment may be proper in such a case where a plaintiff's causation expert has been excluded. (*Lowery v. Kindred Healthcare Operating, Inc.* (2020) 49 Cal.App.5th 119, 121, 262 Cal.Rptr.3d 663.)

In *Jones, supra,* 163 Cal.App.3d 396, 403, 209 Cal.Rptr. 456, the court held that " 'the unknown and mysterious etiology of cancer' is beyond the experience of laymen and can only be explained through expert testimony." (*Id.* at p. 403, 209 Cal.Rptr. 456.) Plaintiffs attempt to distinguish *Jones* by arguing that the issue in that case was *specific* causation—whether the plaintiff's ingestion of an oral contraceptive caused her to develop cancer. (*Id.* at p. 401, 209 Cal.Rptr. 456.) The court's reasoning, however, applies equally to the necessity of expert testimony to explain the causes of heart failure—which, as Dr. Goyal himself testified, is complicated to figure out even for a heart failure doctor. Indeed, admissible expert testimony must first be provided to show "that defendants' products were capable of causing the disease at issue, in anyone. Without any evidence demonstrating the [product] was even capable of causing disease, the experts could not reliably conclude the [product] caused the *plaintiff's* disease, even if other known causes were ruled out." (*Johnson & Johnson Talcum Powder Cases, supra,* 37 Cal.App.5th at p. 330, 249 Cal.Rptr.3d 642.) In general, expert testimony is required to establish general causation in products liability cases. (*In re Mirena IUD Prods. Liab. Litig.* (S.D.N.Y. 2016) 202 F.Supp.3d 304, 310.)

"In contrast, if causation presents a question that is within the common knowledge of persons of ordinary education, then expert testimony is not required." (*Kaney v. Custance* (2022) 74 Cal.App.5th 201, 217, 289 Cal.Rptr.3d 356.) For example, whether the absence of a handrail in a stairway and/or the size of the risers caused plaintiff to fall down the stairs was within common knowledge and therefore did not require expert testimony to establish causation. (*Ibid.*) Likewise, "the question whether the absence of seat belt restraint ... constituted proximate cause of plaintiff's claimed injuries, was one of such common knowledge that persons of ordinary education could reach an intelligent answer." (*McNeil v. Yellow Cab Co.* (1978) 85 Cal.App.3d 116, 118, 147 Cal.Rptr. 733.) Here, however, whether a diabetes medication like saxagliptin is capable of causing heart failure in anyone is beyond the common knowledge of persons of ordinary education. It is a highly complicated issue, as plaintiffs' own experts recognized.

***10** Plaintiffs cite various cases in support of their argument that non-expert evidence can create

a triable issue of material fact as to general causation. These cases, however, do not in fact support plaintiffs' proposition. In *Cooper v. Takeda Pharmaceuticals America, Inc.* (2015) 239 Cal.App.4th 555, 577–578, 191 Cal.Rptr.3d 67, for example, the court confirmed the holding in *Jones, supra*, 163 Cal.App.3d 396, 209 Cal.Rptr. 456, that expert testimony is required to establish causation in cases involving cancer. Moreover, while the court there held that the trial court erred in finding that the epidemiological studies relied on by the expert did not provide reasonable bases for his causation opinion (*Cooper*, at p. 587, 191 Cal.Rptr.3d 67), it is readily distinguishable. The court found that "the trial court's rejection of these studies was too simplistic, because it did not take into account the varied scientific principles involved in determining the validity of the studies." (*Id.* at p. 588, 191 Cal.Rptr.3d 67.) The court further emphasized the importance of considering a body of studies as a whole, because "any one study can be criticized, but if most studies consistently reach a similar answer, that gives confidence to an epidemiologist that the answer is correct."[10] (*Id.* at p. 590, 191 Cal.Rptr.3d 67.) As discussed above, here there have been no subsequent studies done after SAVOR that confirmed the association found between saxagliptin and increased heart failure.

In *Monroe v. Zimmer U.S. Inc.* (E.D.Cal. 2011) 766 F.Supp.2d 1012, 1029–1031, the court held that the plaintiff established a material issue of fact regarding general causation based on admissible testimony from plaintiffs' two causation experts. In *Sellers v. Bayer Healthcare Pharms. Inc.* (W.D.Mo., Feb. 9, 2017, No. 4:14-cv-00954-SRB), 2017 WL 2305006, 2017 U.S. Dist. Lexis 144168, the court, as plaintiffs highlight, found that warning labels on similar drugs created "a genuine issue of material fact concerning Bayer's knowledge of a known or knowable risk in connection with Plaintiff's failure to warn claim." (*Id.* at p. *4, 2017 U.S. Dist. Lexis 144168, at p. *14.) A failure to warn is not the subject of this appeal. With respect to the relevant issue of causation, the court held that the testimony of the plaintiff's *expert* "demonstrat[ed] a significant connection between the conduct that occurred and the injury alleged by plaintiff." (*Id.* at p. *3, 2017 U.S. Dist. Lexis 144168, at p. *10.)

Because expert testimony is required to show general causation in this case, we need not consider plaintiffs' argument that there is substantial non-expert evidence to support general causation.[11] Even if we did consider such evidence, it does not support the claim that saxagliptin can cause heart failure. For example, plaintiffs argue that defendants' updated saxagliptin label admits that saxagliptin is capable of causing heart failure. However, the updated label summarizes the findings from SAVOR and then states: "Consider the risks and benefits of ONGLYZA prior to initiating treatment in patients at a higher risk for heart failure." Likewise, the statements made by SAVOR's authors, which plaintiffs also argue is an admission of causation, cautioned that the unexpected finding of increased heart failure may be a "false positive result" that needs to be further investigated and confirmed in other studies.

***11** Finally, plaintiffs point to statements issued by the AHA and FDA following SAVOR which indicate that saxagliptin may cause or increase the risk of heart failure. These are insufficient to create a triable issue as to general causation. First, neither the AHA nor FDA

explicitly stated that saxagliptin was capable of causing heart failure. Second, the AHA and FDA's statements regarding saxagliptin and heart failure were both based on SAVOR's finding alone which, as discussed above, does not support causation. Logically, any warnings based only on SAVOR also cannot support causation, and plaintiffs cannot attempt to circumvent the shortcomings of SAVOR by pointing to other evidence that merely relies on SAVOR's finding. Again, any opinion as to causation requires expert testimony, which has been excluded here.

3. The Trial Court Did Not Abuse Its Discretion in Denying Plaintiffs' Request for Continuance

Lastly, we review for abuse of discretion the trial court's denial of plaintiffs' request to enlarge discovery deadlines in order to designate a new expert. (*Johnson v. Alameda County Medical Center* (2012) 205 Cal.App.4th 521, 531, 140 Cal.Rptr.3d 281.) We find none here, as plaintiffs were afforded ample time during the first phase of discovery to designate general causation experts and to conduct expert discovery. Plaintiffs designated Dr. Goyal as their only expert to opine that saxagliptin can cause heart failure, and sought to identify a new expert only after Dr. Goyal was excluded. Although the court's decision to exclude Dr. Goyal may have been unexpected to plaintiffs, they made the strategic decision to identify only one expert in this area, despite knowing how crucial it was to prevail on the issue of general causation. The trial court did not abuse its discretion in concluding that allowing plaintiffs to designate a new expert would prejudice defendants given the amount of time and resources needed to conduct additional expert discovery and likely another round of *Daubert*/*Sargon* briefing and hearings.[12]

Disposition

The judgment is affirmed. Defendants shall recover their costs on appeal.

WE CONCUR:

BROWN, P. J.

WHITMAN, J.*

All Citations

--- Cal.Rptr.3d ----, 2023 WL 3001055

Footnotes

* Judge of the Superior Court of California, County of Alameda, assigned by the Chief Justice pursuant to article VI, section 6 of the California Constitution.

1 Saxagliptin is part of a class of diabetes medications known as DPP-4 inhibitors.

2 *Daubert v. Merrell Dow Pharmaceuticals, Inc.* (1993) 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469.

3 "General causation" means that a product is capable of causing the disease at issue in anyone, as distinguished from "specific causation," which means that the product was a substantial factor in bringing about the plaintiff's injury. (See *Johnson & Johnson Talcum Powder Cases* (2019) 37 Cal.App.5th 292, 323–332, 249 Cal.Rptr.3d 642.)

4 *Sargon Enterprises, Inc. v. University of Southern California* (2012) 55 Cal.4th 747, 149 Cal.Rptr.3d 614, 288 P.3d 1237 (*Sargon*).

5 In this same order, the trial court denied plaintiffs' motions to exclude two of defendants' experts, Dr. Suneil Koliwad and Dr. Eric Adler, and granted in part plaintiffs' motion to exclude defendants' expert, Dr. Todd Lee.

6 Plaintiffs initially appealed from the order granting the motion for summary judgment, which is not appealable. A judgment rendered on the order however, was entered nunc pro tunc and was filed on January 27, 2023.

7 All further statutory references are to the Evidence Code unless otherwise specified.

8 At oral argument, plaintiffs' counsel argued that in a subsequent 2014 publication, these same authors noted there was a "statistically significant difference between the 2 [SAVOR] groups after post hoc adjustment for multiple comparisons." However, this same article also reaffirmed the risk of a " 'false positive' result" and that the observation of increased heart failure in saxagliptin users "was unexpected and requires confirmation with several ongoing cardiovascular outcomes trials." Therefore, the publication does not change the calculus about whether the SAVOR study establishes that saxagliptin can cause heart failure.

9 Plaintiffs criticize the trial court for interpreting consistency to require replication despite Dr. Goyal's own admission that replication of the same finding is required in order to find consistency.

10 This consideration further supports the importance of replicating the result of a study before a causal relationship can be established or accepted in the scientific community, as noted in the Reference Guide. (*Reference Guide, supra,* at p. 604.)

11 Plaintiffs have requested that we take judicial notice of the 2022 "Guideline for the Management of Heart Failure" published by the AHA, American College of Cardiology, and Heart Failure Society of America (Guideline). Defendants oppose the request. We deny the request. Plaintiffs acknowledge that we could not properly take judicial notice of the material for the truth of its contents, but fail to articulate in what other way it is relevant to the issues on appeal. Moreover, the Guideline is duplicative of a 2016 statement by the AHA already in the record that noted SAVOR's finding of increased hospitalization for heart failure among saxagliptin users and listed saxagliptin as one of the medications "that may cause or exacerbate HF" based on this finding. The Guideline merely repeats this statement.

12 Plaintiffs' reliance on *Oliveros v. County of Los Angeles* (2004) 120 Cal.App.4th 1389, 16 Cal.Rptr.3d 638 is inapposite, as that case involved a motion to continue trial by a few weeks due to an unexpected trial conflict that had arisen for the defendant's counsel. (*Id.* at p. 1393, 16 Cal.Rptr.3d 638.) The trial court denied the motion despite this showing of good cause and despite having received no objection to this brief continuance from opposing counsel. (*Ibid.*)

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