UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA
CASE NO. 2:17-CV-14302-ROSENBERG/MAYNARD

DENNIS MCWILLIAMS,
LORI MCWILLIAMS,

Plaintiffs,

v.

NOVARTIS AG, *a global healthcare company*,
NOVARTIS PHARMACEUTICALS CORPORATION,
a Delaware corporation,

Defendants.
_____/

ORDER GRANTING IN PART AND DENYING IN PART
DEFENDANT'S MOTION TO EXCLUDE TESTIMONY OF DR. SONAL SINGH

THIS CAUSE is before the Court on Defendant's Motion to Exclude Testimony of Dr. Sonal Singh. DE 56. Defendant seeks to exclude the testimony of Plaintiffs' general causation expert, Dr. Sonal Singh. According to Plaintiffs, Dr. Singh, an epidemiologist, conducted a review of the literature concerning Tasigna and its potential link to vascular disease; found a statistically significant association between Tasigna and all vascular disease after applying a meta-analysis across data from four randomized clinical trials; and, after applying the Bradford Hill causation factors, concluded to a reasonable degree of scientific certainty that Tasigna causes vascular occlusive disease. DE 65. Dr. Singh ultimately reached the conclusion that "to a reasonable degree of scientific certainty, [] nilotinib causes the development of atherosclerotic-related cardiovascular events, including peripheral arterial occlusive disease, ischemic heart disease, and stroke, among patients with chronic myeloid leukemia ('CML')." DE 56-3 at 2.

The Court has carefully reviewed Defendant's Motion, DE 56, Plaintiffs' response, DE 65, Defendant's reply, DE 74, and is otherwise fully advised in the premises. For the reasons set forth below, Defendant's Motion is granted in part and denied in part.

I. FEDERAL RULE OF EVIDENCE 702 AND THE *DAUBERT* STANDARD

Rule 702 of the Federal Rules of Evidence provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed. R. Evid. 702. The proponent of the expert testimony bears the establishing its admissibility. *McDowell v. Brown*, 392 F.3d 1283, 1298 (11th Cir. 2004). In determining whether expert testimony and any report prepared by the expert may be admitted, the Court inquires whether (1) the expert is qualified to testify competently regarding the matters he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable; and (3) the testimony assists the trier of fact, through the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue. *United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) (quoting *City of Tuscaloosa v. Harcros Chems., Inc.*, 158 F.3d 548, 562 (11th Cir. 1998) (citing *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 589 (1993))).

Under *Daubert*, district courts are to perform a "gatekeeping" role concerning the admission of expert testimony. *Daubert*, 509 U.S. at 592–93; *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 150–52 (1999). "The Supreme Court did not intend, however, that the gatekeeper role supplant the adversary system or the role of the jury: vigorous cross-examination,

presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." *McDowell*, 392 F.3d at 1299 (citations omitted).

II. ANALYSIS

Defendant first argues that Dr. Singh's meta-analysis should be excluded because (1) he did not follow his own standard methodology and (2) his meta-analysis relies on unsupported assumptions and methodologic errors. Defendant then argues that the inadmissibility of Dr. Singh's meta-analysis renders his other opinions inadmissible.

I. Dr. Singh's Meta-Analysis

When Dr. Singh conducts a meta-analysis for publication, his general procedure is to "conduct[] a systematic search of publicly available literature, review[] the results to determine which publications are relevant to his analysis, then extract[] data from those publications and finally perform [] a statistical analysis on that data." DE 56 at 6 (citation omitted).

a. Dr. Singh's Methodology

Defendant argues that Dr. Singh did not follow his own standard methodology. First, Defendant notes that, unlike when he prepares a meta-analysis for publication, Dr. Singh did not employ a second scientist to perform the meta-analysis. DE 56 at 6–7. While Dr. Singh normally collaborates with a second scientist, the fact that he did not in this case does not necessarily make his methodology unreliable.

Defendant also notes that Dr. Singh has never before prepared a meta-analysis for the purpose of litigation and that he has not submitted for publication any paper related to his meta-analysis in this case. DE 56 at 7. As other courts have noted, an expert's unwillingness to publish could weigh against the admissibility of the expert's opinions. *See Daubert v. Merrell Dow*

Pharms., Inc., 43 F.3d 1311, 1318, n. 9 (9th Cir. 1995) (*Daubert II*). ("That plaintiffs' experts have been unable or unwilling to publish their work undermines plaintiffs' claim that the findings these experts proffer are 'ground[ed] in the methods and procedures of science' and 'derived by the scientific method.'"). However, "[t]here may well be good reasons why a scientific study has not been published." *Id.* "[T]he standards for courtroom testimony do not necessarily parallel those of the professional publications." *Wendell v. GlaxoSmithKline LLC*, 858 F.3d 1227, 1236 (9th Cir. 2017) (citing *Ambrosini v. Labarraque*, 101 F.3d 129, 138 (D.C. Cir. 1996)).

Here, the Court finds that the fact that Dr. Singh has not published his opinions does not render his testimony inadmissible. The Court's gate-keeping role under *Daubert* is to ensure that only expert testimony that is reliable is admitted. The Court finds that Dr. Singh's methodology is sufficiently reliable. As detailed in his report, Dr. Singh did a systematic review of all of the literature available based on search terms that he developed; he categorized all of the data that was available to him from peer-reviewed sources; he looked at the data from the clinical trials and the observational studies; and, he analyzed all of this data to reach a conclusion about the relationship between Tasigna and atherosclerotic-related cardiovascular events. *See* DE 56-3. Thus, because Dr. Singh's methodology is sufficiently reliable, the fact that he has not sought to publish his work does not render his opinions inadmissible in this case.

b. Dr. Singh's Assumptions

In his meta-analysis, Dr. Singh considered four, non-blinded clinical trials which compared patients treated with Tasigna to patients treated with Gleevec. Defendant makes four arguments as to errors it argues Dr. Singh made. Defendant argues that: (1) Dr. Singh failed to take into account the adjudication of patient-level data; (2) Dr. Singh failed to take into account that Gleevec may be cardio-protective; (3) Dr. Singh failed to distinguish between

cerebrovascular and other adverse events; and (4) Dr. Singh's meta-analysis only relied on non-blinded clinical trials. DE 56 at 8–17. The Court will address each argument in turn.

i. Patient-Level Data

Defendant argues that Dr. Singh did not account for the potential misclassification of adverse event reports in his meta-analysis. DE 56 at 8–11. Defendant argues that, during clinical trials, adverse events may be misclassified by the study physician as the wrong injury; if the events are misclassified, the events would no longer offer support for Dr. Singh's analyses. *Id.* at 5. Defendant notes that in 2014 it convened a panel of outside cardiovascular experts to review the adverse events that Dr. Singh relies upon in his meta-analysis. *Id.* at 9. The "experts concluded that only 29 of the 63 adverse events could be fully confirmed as cardiovascular events and two others were only partially confirmed. The remaining events (more than half of the total relied on in Dr. Singh's analysis) could not be confirmed to be cardiovascular events." *Id.* Defendant notes that Plaintiffs' counsel was aware of this determination but did not make Dr. Singh aware. *Id.*

Plaintiffs respond that:

> as [Dr. Singh] does in every systematic review and meta-analysis, he only considered verified information obtained from reliable public sources. Specifically, Novartis claims he should have considered certain meeting minutes of an internal Novartis-sponsored committee that, many years after the fact, Novartis convened to provide a second opinion on the classification of vascular events determined by clinical investigators in its clinical trials. Notably, the committee confirmed half of the events were properly classified, but were unable to obtain sufficient data to form an opinion on the others. They did *not* identify any events that were misclassified.

DE 65 at 9–10. Plaintiffs note that Dr. Singh did not rely on Plaintiffs' counsel for any material but rather conducted his own independent evaluation of the peer reviewed literature. *Id.* at 10.

The Court agrees with Plaintiffs. As is his standard procedure, Dr. Singh conducted an independent review of the available literature and looked at published and verified literature. *See* DE 56-3. It would be more concerning to the Court if he did not follow his standard procedure and instead relied upon information provided by counsel. Additionally, as Dr. Singh pointed out in his deposition, the conclusion of the independent experts would not impact his review of the data. *See* DE 56-2 ("They were classified as cardiovascular events because that's what the primary studies by report of the New England Journal. So unless I view those as falsification of data, which they aren't, then those are cardiovascular events.").

ii. Gleevec as a Comparator

As both parties note, "it is unethical for Tasigna clinical trials to be designed with a placebo control; instead, the clinical trials involve comparisons between Tasigna and Gleevec." DE 65 at 11. Defendant argues, however, that Dr. Singh "failed to address the growing body of evidence that Gleevec® may be cardio-protective, which would make it an improper comparator for his meta-analysis." DE 56 at 11. Plaintiffs respond that "Dr. Singh did consider this hypothesis, and he found it unsupported and discredited by objective evidence." DE 65 at 11. Dr. Singh did consider the *Giles et al.* study that Defendant notes and found it to suffer from several flaws that it made its conclusions unreliable. *See* DE 56-3 at 24–25. As Plaintiffs note, Dr. Singh also considered studies that show that the rate of vascular events is higher in patients taking Tasigna than in the general population. *See* DE 65 at 12–13.

iii. Cerebrovascular and Other Adverse Events

Defendant argues that Dr. Singh's meta-analysis is flawed because he failed to distinguish between cerebrovascular and other adverse events. DE 56 at 15–16. Defendant states that the only adverse event relevant to his litigation is stroke, a cerebrovascular event, and that

only two of the four studies on which Dr. Singh relied reported cerebrovascular events. *Id.* Defendant argues that Dr. Singh is conflating findings about peripheral arterial occlusive disease and heart events to cover cerebrovascular events as well. *Id.* at 16. Thus, Dr. Singh's analysis is a poor fit for this case. *Id.*

Plaintiffs respond that "[t]his argument is meritless because the literature, health agency reports, and warning labels consistently address all vascular events as a group, implicating a global problem of accelerated atherosclerosis associated with Tasigna that can attack any number of vascular beds." DE 65 at 14.

The Court agrees with Plaintiffs. As Dr. Singh explains:

> Atherosclerosis is an arterial disease which is one of the leading causes of death in the United States. High quantities of LDL cholesterol are considered one of the principal risk factors of the disease, although inflammation may also play a role. The lesions of atherosclerosis occur in the large and medium sized arteries of the heart, brain and extremities which can lead to myocardial infarction, stroke and peripheral arterial disease. The risk factors for atherosclerosis include hyperlipidemia and diabetes as well as genetic predisposition for the disease.

DE 56-3 at 6 (citing Russell Ross, *Atherosclerosis—An Inflammatory Disease*, 340 N. Engl. J. Med., 115, 115–26 (1999)). In the article cited by Dr. Singh, Dr. Ross explains that "[t]he lesions of atherosclerosis occur principally in large and medium-sized elastic and muscular arteries and can lead to ischemia of the heart, brain, or extremities, resulting in infarction." Ross, *supra*, at 115. Atherosclerosis can manifest itself in various different problems. Accordingly, the fact that Dr. Singh looks at the larger problem of atherosclerosis—rather than only looking at incidence of stroke or other cerebrovascular events—does not render his report unreliable.

iv. Non-blinded Clinical Trials

Defendant argues that Dr. Singh's meta-analysis is unreliable because the four randomized clinical trials on which he relied were not blinded and Dr. Singh made no effort to

evaluate whether there was any bias in the results due to the fact that the studies were not blinded. DE 56 at 16–17. Plaintiffs respond that randomized clinical trials are the gold standard for evaluating whether a drug is related to the risk of an adverse condition and the fact that the trials were not blinded does not remove the studies from the gold standard of randomized clinical trials. DE 65 at 14–15.

The Court finds that the fact that the studies on which Dr. Singh relied were not blinded does not make Dr. Singh's meta-analysis unreliable. Dr. Singh only relied upon randomized clinical trials, "the 'gold standard' for determining whether a drug is related to the risk of developing an adverse health outcome." *See In re Bextra and Celebrex Mktg. Sales Practice and Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1173 (N.D. Cal. 2007). While a blinded study may be the ideal to eliminate the risk of bias by the evaluating physicians, that the randomized clinical trials on which Dr. Singh relied were not blinded does not make his meta-analysis unreliable.

II. Dr. Singh's Bradford-Hill Analysis

After his meta-analysis, Dr. Singh conducted a Bradford-Hill analysis to assess causation. "Sir Bradford Hill was a world-renowned epidemiologist who articulated a nine-factor set of guidelines in his seminal methodological article on causality inferences. The Bradford Hill criteria are nine factors widely used in the scientific community to assess general causation." *Jones v. Novartis Pharm. Corp.*, 235 F. Supp. 3d 1244, 1267 (N.D. Ala. 2017) (citations omitted). "While the Eleventh Circuit has not yet directly commented on the Bradford Hill criteria, the reliability of the methodology is strengthened by the number of other circuit courts and district courts within this Circuit who have approved of an expert's use of the criteria." *Id.* at 1268. "[T]he Bradford Hill factors cannot be applied without first establishing a causal association." *Id.*

Defendant argues that Dr. Singh's Bradford-Hill analysis should be excluded because a Bradford-Hill analysis to determine causation is only appropriate after finding a statistically significant association. DE 56 at 17. Defendant argues that because Dr. Singh's meta-analysis is unreliable, his Bradford-Hill analysis also must be rejected. As Dr. Singh found a statistically significant association, DE 56-3 at 6–12, and the Court found that Dr. Singh's meta-analysis is reliable, Dr. Singh's Bradford-Hill analysis is admissible.

III. Dr. Singh's Characterization of the Atherosclerosis-Related Conditions as "Severe" or "Rapidly Progressive"

Defendant seeks to exclude Dr. Singh's opinion that Tasigna is causally related to development of atherosclerosis-related conditions that are "severe" or "rapidly progressive." DE 56 at 17–19. Defendant notes that the only time Dr. Singh describes the atherosclerosis-related conditions as "rapidly progressive" is in the first sentence of his report. *Id.* at 17–18. Defendant also points to Dr. Singh's deposition in which he "acknowledge[s] that he has no statistical support for an opinion that Tasigna® is associated with atherosclerosis that is 'rapidly progressive.'" *Id.* at 18 (citing DE 56-2 at 35:18–36:2; 39:24–40:12). Plaintiffs did not respond to this argument. *See* DE 65. Accordingly, the Court agrees with Defendant that Dr. Singh cannot testify that Tasigna is causally associated with atherosclerosis characterized as "severe" or "rapidly progressive."

III. CONCLUSION

For the foregoing reasons, it is hereby **ORDERED AND ADJUDGED** that Defendant's Motion to Exclude Testimony of Dr. Sonal Singh [DE 60] is **GRANTED IN PART AND DENIED IN PART**. Dr. Singh is permitted to testify; he may not, however, testify that Tasigna is causally associated with atherosclerosis characterized as "severe" or "rapidly progressive."

DONE and ORDERED in Chambers, West Palm Beach, Florida, this 9th day of July, 2018.

ROBIN L. ROSENBERG
UNITED STATES DISTRICT JUDGE

Copies furnished to:
Counsel of Record